Lilly

Fax

Eli Lilly and Company
Lilly Corporate Centre
Indianapolis, Indiana 46285
U.S.A.

Date: 20 September 2004

To: Regina DeBerry,
Company: USPTO
Fax: 703-872-9306 (Tech Ctr. 1600)

From: Paula Davis
Phone: 317-433-3422
Fax: 317-276-5172
Total Pages: 59, including cover sheet

Privileged and Confidential Communication

Subject: **Appeal Brief For Hoffmann and Lu**
Application Number: 09/928,198

If there are any transmittal problems, please contact Jan Fowler at 317-655-1715. This facsimile message is intended only for the individual to whom it is addressed and may contain information that is privileged, confidential or exempt from disclosure under applicable law. If you have received this facsimile in error, please notify us immediately by telephone (collect).

Please type a plus sign (+) inside this box → [+]

PTO/SB/17 (12/97)

Approved for use through 09/30/00. OMB 0651-0032

Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

FEE TRANSMITTAL

Note: Effective November 10, 1998.
Patent fees are subject to annual revision.

TOTAL AMOUNT OF PAYMENT $440.00

Complete if Known	
Application Number	09/928,198
Filing Date	August 10, 2001
First Named Inventor	James A. Hoffmann and Jirong Lu
Group Art Unit	1647
Examiner Name	R. DeBerry
Attorney Docket Number	X-12383N

METHOD OF PAYMENT (check one)

1. [X] The Commissioner is hereby authorized to charge indicated fees and credit any overpayments to:

Deposit Account Number: 05-0840

Deposit Account Name: Eli Lilly and Company

[X] Charge Any Additional Fee Required Under 37 CFR 1.16 and 1.17

[ ] Charge the Issue Fee Set in 37 CFR 1.18 at the Mailing of the Notice of Allowance

2. [ ] Payment Enclosed:

[ ] Check [ ] Money Order [ ] Other

FEE CALCULATION

1. FILING FEE

Large Fee Code	Entity Fee ($)	Small Fee Code	Entity Fee ($)	Fee Description	Fee Paid
101	770	201	385	Utility filing fee	
106	340	206	170	Design filing fee	
107	520	207	265	Plant filing fee	
108	770	208	385	Reissue filing fee	
114	160	214	80	Provisional filing fee	

SUBTOTAL (1) ($) 0

2. CLAIMS

	Extra	Fee from below	Fee Paid
Total Claims -20**=		X 18 =	
Independent Claims -3**=		X 86 =	
Multiple Dependent Claims (first time)		290 =	

Large Fee Code	Entity Fee ($)	Small Fee Code	Entity Fee ($)	Fee Description
103	18	203	9	Claims in excess of 20
102	86	202	43	Independent claims in excess of 3
104	290	204	145	Multiple dependent claim
109	86	209	43	Reissue independent claims over original patent
110	18	210	9	Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Fee Code	Entity Fee ($)	Small Fee Code	Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge-late filing fee or oath	
127	50	227	25	Surcharge-late provisional filing fee or cover sheet.	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	110.
116	420	216	210	Extension for reply within second month	
117	950	217	475	Extension for reply within third month	
118	1,480	218	740	Extension for reply within fourth month	
128	2,010	228	1,005	Extension for reply within fifth month	
119	330	219	165	Notice of Appeal	
120	330	220	165	Filing a brief in support of an appeal	330.
121	290	221	145	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive-unavoidable	
141	1,330	241	665	Petition to revive-unintentional	
142	1,330	242	665	Utility issue fee (or reissue)	
143	480	243	240	Design Issue Fee	
144	640	244	320	Plant Issue Fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	180	126	180	Submission of Information Disclosure Stmt.	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	770	246	385	Filing a submission after final rejection (37 CFR 1.129(a))	
149	770	249	385	For each additional invention to be examined (37 CFR 1.129(b))	
179	770	279	385	Request for Continued Examination (RCE)	
169	900	169	900	Request for expedited examination of a design application	

Other fee (specify) Terminal Disclaimer 1.321

Other fee (specify)

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) $440.00

SUBMITTED BY

Complete (if applicable)

Typed Name	Paula K. Davis	Reg. Number	47,517
Signature	Paula K. Davis	Date	Sept. 20, 2004

CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below.

Paula Davis

Type or print name of person signing certification

RECEIVED
CENTRAL FAX CENTER

SEP 20 2004

CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below.

Paula K. Davis
Type or print name of person signing certification

Paula K. Davis Sept. 20, 2004
Signature Date

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Before the Board of Patent Appeals and Interferences

Appellants	:	James A. Hoffmann & Jirong Lu	
Serial No.	:	09/928,198	Group Art Unit: 1647
Filed	:	August 10, 2001	
For	:	FSH FORMULATION	Examiner: R. DeBerry
Docket No.	:	X-12383N	

BRIEF FOR HOFFMANN & LU

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants appeal from the final rejection dated March 18, 2004, of Claim 128 of this application.

Real Party in Interest

Eli Lilly and Company is the Real Party in Interest.

Related Appeals and Interferences

There are no related appeals or interferences.

Status of Claims

Claims 1-127, previously submitted in this case, have been cancelled. Claim 128

was presented and stands finally rejected under 35 U.S.C. § 103 and obviousness-type double patenting over co-pending application 09/744,431 (the '431 application).

Status of Amendments

An amendment, adding three new claims dependent from Claim 128, was presented on May 18, 2004. An advisory action mailed July 12, 2004, denied entry of the amendment.

Summary of Claimed Subject Matter

The present invention provides a novel pharmaceutically acceptable, solution formulation of FSH and benzyl alcohol. Being a preserved solution formulation, the invention avoids reconstitution of the lyophilized protein multiple times over the course of therapy. Reconstitution requires a specific technique, often causing problems for patients. If done improperly, the concentration of drug in the reconstituted solution may be incorrect, resulting in too little or too much drug being administered. Furthermore, because the reconstituted solution cannot be stored and used over the course of therapy, each administration results in a portion being discarded. *See* Gonal-F package insert, Appellants' IDS reference CV. This is wasteful and costly. Because it is a multi-dose solution product, the instant invention represents a significant advance over prior art formulations of FSH.

Specifically, Claim 128 provides a pharmaceutically acceptable, solution formulation comprising human FSH (p. 10, line 9) and benzyl alcohol in an aqueous diluent (p. 6, lines 13-20), wherein (a) the concentration of FSH is 5.0 μg/mL to 2 mg/mL (p. 35, lines 8-9), (b) the FSH consists of an α-subunit (SEQ ID NO:5, p. 13, lines 14-16) and a β-subunit (SEQ ID NO:6, p. 13, lines 17-19), held together by noncovalent interactions (p. 3, lines 14-16), and (c) the formulation is suitable for multi-dose administration by injection (p. 7, line 7; p. 40, lines 28-35).

Grounds of Rejection to Be Reviewed on Appeal

(1) Whether Claim 128, which relates to the solution formulation comprising low concentrations of human FSH and benzyl alcohol is patentable under 35 U.S.C. § 103 over three references: (a) Keene *et al.*, which describes human FSH sequences; (b) Andya *et al.*, which generally describes lyophilized proteins which are reconstituted at a high concentration ($\geq$ 50 mg/mL) and may be optionally preserved; and (c) Skrabanja *et al.*, which explicitly

describes specific solution formulations of gonadotropins, but does not teach the use of any preservative.

(2) Whether Claim 128 is patentable over copending application 09/744,431 because the Appellants have offered to file a terminal disclaimer in the instant case.

As only one claim, Claim 128, stands in this case, no grouping is required.

Argument

Claim 128 was rejected under 35 U.S.C. § 103 as being unpatentable over Keene *et al.*, Journal of Biological Chemistry 264(9): 4769 (1989) [hereinafter Keene] in view of Skrabanja *et al.*, EP 0 853 945 (IDS reference BF) [hereinafter Skrabanja] and Andya *et al.*, U.S. Pat. No. 6,267,958 [hereinafter Andya].

The rejection of Claim 128 is improper for several reasons. Section I of this brief will demonstrate that the Examiner failed to construct a *prima facie* case of obviousness. First, the Examiner improperly picked and chose elements of the claimed invention from the prior art to reconstruct the invention in hindsight, using the present application as the motivation for combining rather than finding the motivation for combining in the references themselves. Second, the Examiner ignored the art teaching that aqueous solutions of FSH are unstable. Third, the Examiner failed to acknowledge that the ordinarily skilled artisan knew that adding preservatives to solutions having a low concentration of protein, at best, is unpredictable and with some proteins, was thought to destabilize the protein. Thus, Section I establishes that Claim 128 is not *prima facie* obvious over the combination of references cited by the Examiner.

Section II provides compelling evidence, even if a *prima facie* case is established, that the claimed invention is not obvious. Because for about thirty years prior to the present invention the treatment regimen for FSH required the patient to reconstitute one or more doses per day over a period of about two weeks, a long-felt but unresolved need existed for a preserved aqueous FSH formulation suitable for multi-dose administration by injection for at least thirty years. This is compelling contemporaneous evidence that what the Examiner asserts to be obvious, based on "general knowledge," indeed was not obvious. The stability of low concentrations of FSH formulated with benzyl alcohol is unexpected in view of the prior art of record and, when FSH solutions preserved with benzyl alcohol were introduced for sale, they

quickly demonstrated commercial success. These secondary considerations rebut any *prima facie* showing and provide compelling evidence of patentability. Thus, by summarily dismissing or ignoring such evidence, the Examiner has improperly maintained the rejection of Claim 128. For these reasons, the instant invention is not obvious, and thus, the rejection is inappropriate.

I. THE PRIOR ART DOES NOT PROVIDE THE REQUISITE TEACHING, SUGGESTION, OR MOTIVATION TOWARD THE CLAIMED FORMULATION, NOR DOES IT PROVIDE A REASONABLE EXPECTATION OF SUCCESS, AND THUS, IT FAILS TO SUPPORT A *PRIMA FACIE* CASE OF OBVIOUSNESS.

The burden of proving a *prima facie* case of obviousness is on the Patent Office. *In re Bell*, 991 F.2d 781, 783, 26 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1993). According to the M.P.E.P.:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

M.P.E.P. § 2143 (8th ed. 2001). The references cited do not create a *prima facie* case of obviousness.

"Obviousness is tested by 'what the combined teachings of the references would have suggested to those of ordinary skill in the art.'" *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1599 (Fed. Cir. 1988) (quoting *In re Keller*, 642 F.2d 413, 425, 208 U.S.P.Q. 871, 881 (C.C.P.A. 1981)). "[T]eachings of references can be combined *only* if there is some suggestion or incentive to do so." *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984). The PTO can satisfy its burden of establishing a *prima facie* case of obviousness "only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *Fine*, at 1074. In the present case, the Examiner has not met this burden, and thus, the rejection of Claim 128 is inappropriate.

Claim 128 provides a solution formulation comprising low concentrations of human FSH and benzyl alcohol in an aqueous diluent. The claim limits the formulation such that

it must have a human FSH concentration in the range of 5.0 μg/mL to 2 mg/mL, it must contain specific α- and β-subunit protein sequences corresponding to human FSH that are held together by non-covalent bonds, and it must be suitable for multi-dose administration by injection.

The Examiner alleges that Claim 128 is unpatentable over three pieces of art: Keene, Skrabanja, and Andya, *supra*. Regarding motivation to combine the references, the Examiner states:

> The motivation and expected success is [sic] provided by Skrabanja and Andya. Skrabanja *et al.* teach pharmaceutical formulations comprising FSH which can be used in stable multi-use liquid pharmaceutical formulations. Andya *et al.* teach that pharmaceutical multi-use formulations comprising FSH can have preservatives such as benzyl alcohol to reduce bacterial action.

Final Rejection, p. 6. Additionally, the Examiner asserts that "suggestion or motivation can be found . . . *in the general knowledge available to one skilled in the art* . . . . The addition of preservatives to pharmaceutical formulations is deemed routine and well within the purview of the skilled artisan." Final rejection, p. 7 (emphasis in original). Yet, the **Examiner provides no objective evidence** that teaches, suggests, or motivates one to combine the cited references. "Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chem. Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

"Determining whether there is a suggestion or motivation to modify a prior art reference is one aspect of determining the scope and content of the prior art, a fact question subsidiary to the ultimate conclusion of obviousness." *Sibia Neurosciences, Inc. v. Cadus Pharm., Inc.*, 225 F.3d 1349, 1356, 55 U.S.P.Q.2d 1927, 1931 (Fed. Cir. 2000). To establish the modifications to the art that are needed, one must also determine the differences between the prior art and the instant invention. In brief, the instant invention provides a solution formulation of human FSH, at a specific concentration, preserved with benzyl alcohol, such that it is suitable for multi-dose administration by injection. None of the cited references provide such a formulation or suggest combination with another reference to provide such. A detailed look at the references follows.

A. Skrabanja

Skrabanja describes problems associated with the stability of FSH, indicating that this instability led to FSH being supplied as a lyophilized product that must be reconstituted. Skrabanja notes:

> **The stability of proteins in aqueous formulations is generally a problem in [the] pharmaceutical industry. Likewise the stability of aqueous solutions of the gonadotropins is insufficient to allow storage for longer times. This is especially true for preparations containing the very pure gonadotropins, prepared using recombinant DNA methods, in relatively dilute solutions.** Usually therefore those preparations are stored in a dry form, as is obtained after lyophilization.

Skrabanja, p. 2, lines 42-45 (emphasis added). It discusses different means used in the prior art as attempts to stabilize liquid protein formulations, and then comments on their failures. *Id.* at p. 3, lines 6-14. Skrabanja provides a solution to the stability problem: a "formulation which comprises a gonadotropin and stabilising amounts of a polycarboxylic acid or a salt thereof and of a thioether compound. The gonadotropin-containing formulations of [Skrabanja] have improved stability on prolonged storage in comparison with formulations in which the thioether is lacking." *Id.* at p. 3, lines 15-18.

Skrabanja explicitly describes the claimed excipients (the particular carboxylic acids and thioether compounds) and optional excipients (non-reducing sugars "such as sucrose or trehalose" and non-ionic surfactants) used in its formulation, and is complete in its teaching. For example, on page 4, lines 23 through 33, Skrabanja sets out a nonionic surfactant such as Polysorbate 20, Polysorbate 80, Brij 35, or Pluronic F123 as an optional and preferred embodiment. Also, on page 4, lines 46 to 48, Skrabanja specifies the type of water to be used, and even notes that "small amounts" of a water miscible solvent may be included as co-solvent. **Despite the thoroughness of its description of the formulations, Skrabanja never mentions, suggests, or motivates adding an antimicrobial preservative as an optional excipient.**

Skrabanja's examples are similarly complete, specifying the identity and amount of each and every excipient, including even the "q.s." volume (*quantum sufficit*: the total volume of the sample after water was added, labeled "water to" in Tables I and III, pp. 6 and 7). Such specificity indicates that no other excipients are present in the formulation. No antimicrobial

preservatives, such as benzyl alcohol, are included in the examples. The examples measure the "retainment of in-vitro bioactivity of FSH compositions" (*i.e.*, the stability) over two months at four different temperatures. The samples were stored in closed 2 mL cartridges. These examples were designed to demonstrate, and did demonstrate, that formulations without methionine were less stable than those with methionine. Nonetheless, **Skrabanja's stable formulation, in a "cartridge for multiple use," did not contain** an antimicrobial preservative such as **benzyl alcohol. The teaching is so complete and detailed that this reference lacks the necessary suggestion or motivation to add any unnamed excipient.** In fact, such thoroughness provides a strong suggestion and motivation **not to add** another unnamed excipient.

The Examiner stresses that Skrabanja provides a "cartridge for multiple use." Yet, when taken in context, Skrabanja's use of the term **"multiple use" neither means nor suggests that the product is preserved, should be preserved, or even could be preserved.** As shown above, the examples of Skrabanja explicitly named every ingredient in the formulation and were stored in "cartridges for multiple use," but did not contain a preservative. Moreover, according to the "Note for Guidance on Maximum Shelf-Life for Sterile Products for Human Use After First Opening or Following Reconstitution," an **unpreserved, sterile product may be used multiple times so long as the in-use stability has been established.** *See European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products (CPMP)*, Guidance CPMP/QWP/159/96, 1999 (emphasis added), reference CCC. Typically, the unpreserved product would not be used for more than 24 hours when stored at 2-8°C, unless reconstitution or dilution occurred under controlled and validated aseptic conditions. *Id.* Within this 24-hour period, a formulation may be administered multiple times, thus making it "multiple use." Although Skrabanja makes no mention of any preservative despite a very detailed and comprehensive teaching, it clearly specifies that its formulations are "sterile." Skrabanja, p. 4, lines 45 and 54; p. 5, lines 21 and 27; and Claim 13. Thus, Skrabanja's sterile formulation, although unpreserved, could be considered a multiple use product. Skrabanja provides no teaching, motivation, or suggestion to add any preservative generally or benzyl alcohol specifically to a liquid FSH formulation.

While Skrabanja goes to great lengths to explicitly spell out its sterile, yet unpreserved, formulation, the **Examiner fails to provide any evidence** explaining why a person of ordinary skill in the art would alter Skrabanja's stable formulation. Skrabanja is explicit in

every detail, explaining how to stabilize a formulation of an unstable protein. Yet, to explain why a person of ordinary skill in the art would be motivated to change the formulation, the Examiner casually states that it comes from "knowledge generally available" and that it is "routine" to add preservatives to protein formulations, with no objective evidence or comment rebutting what is *explicitly* taught in the art—that preservative compatibility is generally unpredictable, that the art explicitly suggested that gonadotropins, particularly FSH, were unstable when formulated at low concentrations, and that FSH was incompatible with preservatives other than thymol (*see* discussion in section II.D, p. 13, *infra*). Such a response does not meet the Examiner's burden to establish a *prima facie* case of obviousness.

B. Andya

Andya provides a stable lyophilized protein formulation that can be reconstituted with a diluent, optionally containing a preservative, to generate a multi-use formulation with very high protein concentration. Andya's invention requires the addition of certain excipients, namely a lyoprotectant such as sucrose or trehalose, such that the lyophilized protein formulations are stable upon storage. Andya also notes that upon reconstitution of the dry powder, the formulation is stable "for at least the time over which it will be administered to a patient." Andya, col. 1, lines 55-59. Thus, Andya describes certain lyoprotectants that provide stability to freeze dried protein formulations but also teaches to limit the use of the reconstituted protein to the period of time over which the protein is administered to the patient (a period generally shorter than the shelf-life required to manufacture, distribute, store, and finally administer a solution).

The object of Andya is to provide a lyophilized formulation that, when reconstituted, provides a very high protein concentration. In fact, Andya requires a concentration greater than or equal to 50 mg protein/mL diluent (more than 25 times the upper limit of FSH concentration in the instant application and more than 10,000 times the lower limit). It does not teach or suggest that a lower concentration protein formulation would be stable.

Andya provides an extensive list of more than 100 proteins that may be used in the lyophilized formulation.

> Examples of proteins encompassed within the definition herein include mammalian proteins, such as, *e.g.*, growth hormone, including **human growth hormone** and bovine

> growth hormone; growth hormone releasing factor; parathyroid hormone; thyroid stimulating hormone; lipoproteins; α-1-antitrypsin; insulin A-chain; insulin B-chain; proinsulin; **follicle stimulating hormone**; calcitonin; luteinizing hormone; glucagon; clotting factors such as factor VIIIC, factor, tissue factor, and von Willebrands factor; anti-clotting factors such as Protein C; atrial natriuretic factor; lung surfactant; a plasminogen activator, such as urokinase or tissue-type plasminogen activator (t-PA); bombazine; thrombin; tumor necrosis factor-α and -β; enkephalinase; RANTES (regulated on activation normally T-cell expressed and secreted); human macrophage inflammatory protein (MIP-1-α); serum albumin such as human serum albumin; mullerian-inhibiting substance; relaxin A-chain; relaxin B-chain; prorelaxin; mouse gonadotropin-associated peptide; DNase; inhibin; activin; vascular endothelial growth factor (VEGF); receptors for hormones or growth factors; an integrin; protein A or D; rheumatoid factors; a neurotrophic factor such as bone-derived neurotrophic factor (BDNF), neurotrophin-3, -4, -5, or -6 (NT-3, NT-4, NT-5, or NT-6), or a nerve growth factor such as NGF-β; platelet-derived growth factor (PDGF); fibroblast growth factor such as aFGF and bFGF; epidermal growth factor (EGF); transforming growth factor (TGF) such as TGF-α and TGF-β, including TGF-β1, TGF-β2, TGF-β3, TGF-β4, or TGF-β5; **insulin-like growth factor-I** and -II (IGF-I and IGF-II); des(1-3)-IGF-I (brain IGF-I); insulin-like growth factor binding proteins; CD proteins such as CD3, CD4, CD8, CD19 and CD20; erythropoietin (EPO); thrombopoietin (TPO); osteoinductive factors; immunotoxins; a bone morphogenetic protein (BMP); an interferon such as **interferon-α, -β, and -γ**; colony stimulating factors (CSFs), *e.g.*, M-CSF, GM-CSF, and G-CSF; interleukins (ILs), *e.g.*, IL-1 to IL-10; superoxide dismutase; T-cell receptors; surface membrane proteins; decay accelerating factor (DAF); a viral antigen such as, for example, a portion of the AIDS envelope; transport proteins; homing receptors; addressins; regulatory proteins; immunoadhesins; antibodies; and biologically active fragments or variants of any of the above listed polypeptides.

Andya, col. 6, line 45 to col. 7, line 16 (emphasis added). FSH is one protein on this broad list. Furthermore, only two proteins are exemplified in Andya: the antibodies anti-HER2 and anti-IgE.

A preservative is mentioned as an **optional** excipient in the diluent used for reconstitution. Andya, col. 17, lines 29-37. Andya does not describe any stability effects of the preservative and later notes that "[t]he amount of preservative is determined by assessing

different preservative concentrations for compatibility with the protein and preservative efficacy testing." Andya, col. 17, lines 32-34. Fourteen preservatives are listed for possible use. Benzyl alcohol is listed as preferred, presumably because it is the preservative used in the exemplified formulations of anti-HER2 and anti-IgE.

Andya is clearly directed to formulations of anti-HER2 and anti-IgE. Andya's invention is the use of certain lyoprotectants to stabilize the dry powder protein formulation. The mere fact that Andya contains a long list of proteins for possible use in its invention does not teach, motivate, or suggest to the person of skill in the art that all proteins in the list can be formulated with all the other excipients disclosed in the patent, particularly all of the optional excipients, including the preservatives listed. Moreover, it does not teach, motivate, or suggest that all the formulations that could be prepared from picking and choosing from the various lists in Andya will yield a stable formulation for all of the proteins, especially considering that the main thrust of Andya is a very high protein concentration, whereas the present invention involves very low protein concentrations.

In fact, the addition of a preservative to some protein formulations has been shown to have a destabilizing effect on physical properties of the protein. For example, benzyl alcohol, Andya's preferred preservative and the preservative used in the instant invention, has been shown to have a destabilizing effect on human growth hormone (Maa and Hsu, *Intl. J. Pharm.* 140:155-58 (1996), Appellants' IDS reference CBU); on human interferon-gamma (Lam *et al.*, *Pharm. Res.* 14(6):725-29 (1997), reference CAC); on interleukin-1 receptor (Remmele *et al.*, *Pharm. Res.* 15(2):200-08 (1998), reference CAA); and on human insulin-like growth factor I (Fransson *et al.*, *Pharm. Res.* 14(5):606-12 (1997), reference CAB). **Three of these proteins are named in Andya's list**: human growth hormone (col. 6, line 46), interferon-gamma (col. 7, lines 8-9), and insulin-like growth factor (col. 7, line 4), **despite the fact that they do not form stable formulations when benzyl alcohol is added**. Thus, Andya lacks both motivation to combine and expectation of success in combining with the other references.

The references cited in the previous paragraph alone are ample evidence that one skilled in the art would plainly recognize that all proteins on Andya's list are not compatible with all the other excipients disclosed, particularly preservatives, and would not be motivated to pick and choose FSH and benzyl alcohol from the list of proteins and the list of optional excipients, respectively, as the Examiner has done. FSH is not an obvious choice for a liquid protein

formulation preserved with benzyl alcohol. Yet again, the Examiner provides no evidence to support her allegation of obviousness. Even though it was known and immediately apparent to a skilled artisan that some of the 100-plus proteins in Andya's list would not be compatible with some of the optional excipients, the Examiner does not address this knowledge of destabilizing effects. Instead, she alleges that is it "routine and well within the purview of the skilled artisan" to add a preservative to a pharmaceutical formulation. She provides no explanation of why FSH and benzyl alcohol, both selected from long lists, would be expected to be compatible. Nor does she explain why the skilled artisan would be compelled to change the high concentrations of Andya to low concentrations, where FSH is especially susceptible to instability. A generic and unsupported statement that it is "knowledge generally available to one skilled in the art" is not sufficient to meet the Examiner's requirement to provide objective evidence showing suggestion, motivation, or teaching to combine, or an expectation of success.

Moreover, the **knowledge generally available** to one skilled in the art of protein formulation science **suggests unpredictability and compatibility problems** between preservatives and proteins. "Any formulator of a protein or peptide dosage form likely has experienced compatibility problems in attempting to develop multi-dose biopharmaceutical products." Akers, *J. Pharm. Sci.* 91(11):2283, 2294 (2002), reference CBW. As noted in *Remington's Pharmaceutical Sciences*, p. 1550 (Gennaro *et al.* eds., 1990), "Antimicrobial agents must be studied with respect to compatibility with all other components of the formula. In addition, their activity must be evaluated in the total formula. It is not uncommon to find that a particular agent will be effective in one formulation but ineffective in another." The addition of a preservative to a protein formulation is anything but "routine." Much experimentation is needed to determine which preservative, **if any**, can successfully be used in the formulation without causing too much degradation. Furthermore, this unpredictability and compatibility is even more acute with FSH, which is known to be unstable, especially in dilute solutions. *See* Skrabanja, p. 3, lines 53-54.

The skilled person, with knowledge of the degradative effect of preservatives on proteins and the unpredictability as to working combinations, simply would have no expectation of success for each and every combination of proteins and excipients disclosed in Andya. Andya also provides no expectation of success for combinations of FSH with benzyl alcohol, especially for a combination having an FSH concentration far lower than Andya teaches. Moreover, Andya

lacks any teaching, motivation, or suggestion to combine it with Skrabanja and Keene.

C. Keene

Keene *et al.* do not teach, suggest, or motivate a person of skill in the art to make any formulation of FSH. Keene simply provides the sequence of human FSH and how to express it recombinantly.

D. Combination of the Cited References: Keene, Skrabanja, and Andya

"The mere fact that it is *possible* to find two isolated disclosures which might be combined in such a way to produce a new compound does not necessarily render such production obvious unless the art also contains something to suggest the desirability of the proposed combination." *In re Bergel*, 292 F.2d 955, 956-57, 130 U.S.P.Q. 206, 208 (C.C.P.A. 1961) (emphasis in original).

The present case is similar to *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). In *Fine*, the Examiner combined three prior art references, substituting portions from each reference, to recreate Fine's invention. However, none of the references taught, suggested, or motivated one skilled in the art to combine the references. The court noted, "[T]he decisionmaker must step backward in time and into the shoes worn by [a person having ordinary skill in the art] when the invention was unknown and just before it was made." *Id.* at 1073 (quoting *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1566, 1 U.S.P.Q.2d 1593, 1595-96 (Fed. Cir. 1987)). Reversing the board's finding of obviousness, the court held that "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to depreciate the claimed invention." *Id.* at 1075.

In the case at hand, the Examiner performed a similar hindsight reconstruction and ignored the general knowledge in the art and specific teachings in the references relied upon that taught against combining the references. Keene contains the sequences for human FSH, but no suggestion for a formulation. Skrabanja provides a stable liquid FSH formulation, but no preservative. A preservative is an optional ingredient in Andya, which provides a lyophilized protein that can be reconstituted to yield a liquid that is 25 to 10,000 times more concentrated than the instant invention. Moreover, both FSH and benzyl alcohol must be selected from extensive lists from which it was known that not all combinations would be operable.

Nonetheless, the Examiner picked only those portions needed to construct the instant invention, and then alleged that the invention was obvious.

Of course, the motivation need not be explicit in the cited references; as the Examiner asserts, suggestion or motivation can be found in the general knowledge available to one skilled in the art. Yet, in this case, the knowledge generally available to one skilled in the art of protein formulation science suggested that the addition of an antimicrobial preservative, such as benzyl alcohol, to a protein in inherently unpredictable in that preservative compatibility must be assessed with each protein-preservative combination. However, in this case, the art *explicitly* taught the addition of a preservative to FSH would lead to degradation, especially in a low concentration solution formulation. Skrabanja expressly teaches that the "stability of proteins in aqueous formulations is generally a problem . . . ." Skrabanja, p. 2, line 42. In addition, Donaldson (U.S. Pat. No. 5,162,306, IDS reference AA) expressly suggests that **preservatives other than thymol may be incompatible** with FSH. *See* col. 25, lines 63-67. There is simply no motivation to combine Skrabanja with Andya or other references that generally teach the use of benzyl alcohol. The specific teachings of Skrabanja and Donaldson clearly point the reader away from such combinations.

Also in the general knowledge was the fact that many FSH products for use in humans were on the market or were introduced over a period of more than thirty years prior to the present invention. None of these products were multi-dose products, and none contained a preservative, despite the fact that all were intended to be administered multiple times to each patient who received them. The fact that all of these FSH formulations were provided in lyophilized form for reconstitution immediately before use strongly suggested to a person of ordinary skill in the art either that FSH was unstable in solution or that it could not be stably formulated with a preservative. *See* Beals, paragraphs 41 and 68. The Examiner failed to consider any of this knowledge as general knowledge in the art.

Attempts to stabilize FSH in solution have been published, such as Samaritani (U.S. Patent No. 5,650,390, col. 1, lines 19-22, IDS reference AF; "It is known that highly purified proteins are time-unstable and are stabilized, for instance, in admixture with saccharides, such as lactose and mannitol or else with proteins and amino acids, such as albumin and glycine.") and Boime (U.S. Patent No. 6,238,890, col. 4, lines 18-20, IDS reference AR; "The single-chain forms of the heterodimers or homodimers have a number of advantages over their

dimeric forms. . . . [T]hey are generally more stable."). References such as these demonstrate the instability of FSH, especially in solution formulations, and the extent to which scientists had previously attempted to resolve the instability problem. *See* Beals, paragraph 72. Thus, the Examiner performed a similar hindsight reconstruction and ignored the general knowledge in the art and specific teachings in the references relied upon that taught against combining the references.

E. Conclusion

In summary, the rejection of Claim 128 as unpatentable over Keene in view of Skrabanja and Andya can only be made through hindsight reconstruction, and therefore is inappropriate. These references lack any express or implied teaching, suggestion, or motivation of combination, and even if combined, no reasonable expectation of success exists. Nor does the general knowledge of one skilled in the art suggest such combination. In fact, general knowledge urges caution and skepticism about adding preservatives to proteins. Thus, the Examiner has failed to establish a *prima facie* case of obviousness.

II. THE PRESERVED FSH FORMULATIONS OF THE INSTANT APPLICATION ARE NOT OBVIOUS BECAUSE THEY FULFILLED A LONG-FELT BUT UNRESOLVED NEED FOR MULTI-DOSE, PRESERVED FSH SOLUTIONS AND THE CONFORMATIONAL STABILITY WAS UNEXPECTED.

A determination of non-obviousness requires the Board to evaluate a number of factors related to the invention. These include: (1) scope and content of the prior art; (2) differences between the prior art and the claims in issue; (3) level of skill in the pertinent art; and (4) evidence of secondary considerations." *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). "Under *Graham*, objective evidence of nonobviousness includes commercial success, longfelt but unresolved need, failure of others, and copying. When present, such objective evidence must be considered. It can be the most probative evidence of nonobviousness in the record, and enables the district court to avert the trap of hindsight." *Custom Accessories Inc. v. Jeffrey-Allan Indus. Inc.*, 807 F.2d 955, 960, 1 U.S.P.Q.2d 1196, 1199 (Fed. Cir. 1986). In the present case, Appellants have presented a wealth of compelling objective evidence of non-obviousness. None of this compelling objective evidence has been considered or rebutted by the Examiner; it has only been summarily dismissed. The Appellants' objective evidence of record

compels a conclusion of non-obviousness.

A. Scope and Content of the Prior Art

The prior art contains several attempts to formulate protein solutions. *See* Skrabanja, p. 2, lines 6-12. As Skrabanja noted, protein solutions of gonadotropins were desired to avoid having to reconstitute the protein immediately prior to injection; nonetheless, such solutions were known to be unstable. *Id.* at lines 13-14. Different stabilizing techniques were attempted, including the addition of citrate, the addition of a non-reducing sugar (e.g., mannitol), and the addition of polycarboxylic acids, yet none of these solutions were physically stable for months at room temperature. *Id.* at lines 6-12. Skrabanja taught that the addition of a polycarboxylic acid and a thioether to the protein solution yields a physically stable formulation. *Id.* at lines 15-18. Nevertheless, because none of these formulations contained a preservative, they lacked the microbiological stability needed for long-term use or storage as a solution.

Andya generally disclosed highly concentrated protein solutions containing optional ingredients such as preservatives. However, preservatives were known to cause degradation of proteins in solution formulations. Indeed, a number of the one hundred-plus proteins listed in Andya were incompatible with preservatives.

Skrabanja and Andya must be read in the context of other prior art. As noted, Maa, Lam, and Fransson, *supra*, specifically addressed the destabilizing effects of preservatives on three proteins listed among Andya's list of possible proteins. Donaldson expressly suggested that preservatives other than thymol are incompatible with FSH ("Of the 24 antimicrobial preservatives listed on Page 1491 of U.S.P. XXI, and U.S.P. and NF Pharmaceutical Ingredients, Thymol (5-methyl-2(1-methylethyl) phenol) was found to be compatible with FSH." *Id.*, col. 25, lines 63-67). Benzyl alcohol is one of the "24 antimicrobial preservatives" listed on page 1491 of the U.S.P.

B. Differences Between the Prior Art and the Claimed Invention

The instant invention is limited to aqueous solutions of human FSH at low concentrations (5.0 μg/mL to 2 mg/mL), preserved with benzyl alcohol, suitable for multi-dose administration by injection. The prior art contained aqueous solutions of human FSH at low concentrations that were either: (1) not preserved (Skrabanja), or (2) preserved with thymol

(Donaldson) and taught away from using other preservatives such as benzyl alcohol. The prior art also discloses extremely high concentration lyophilized formulations of a long list of proteins that might optionally be preserved after assessing for compatibility with the protein (Andya). Conversely, the prior art did not disclose or suggest human FSH aqueous formulations at low concentrations, preserved with benzyl alcohol, suitable for multi-dose administration by injection.

C. Level of Skill in the Art

The relevant level of skill in the art would be an individual with a degree in a chemical or biological science, with experience and competence in protein formulation. The artisan is familiar with the instability associated with low concentration protein solutions, is familiar with specific proteins described in the prior art as being unstable with preservatives, and the degradation that can occur when an antimicrobial preservative is added.

D. Evidence of Long-felt but Unresolved Need

"The existence of an enduring, unmet need is strong evidence that the invention is novel, not obvious, and not anticipated. If people are clamoring for a solution, and the best minds do not find it for years, that is practical evidence . . . of the state of knowledge." *In re Mahurkar Double Lumen Hemodialysis Catheter Patent Litigation*, 831 F. Supp. 1354, 1377-78, 28 U.S.P.Q.2d 1801, 1819 (N.D. Ill. 1993), *aff'd*, 71 F.3d 1573, 37 U.S.P.Q.2d 1138 (Fed. Cir. 1995).

The case *Minnesota Mining and Manufacturing Co. v. Johnson and Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 24 U.S.P.Q.2d 1321 (Fed. Cir. 1992), clearly demonstrates the concept of long-felt need. In that case, inventors from three competitors avidly attempted to create improved casting materials for orthopedics. To demonstrate the need, as well as the failure to previously resolve the need, the court described each incremental step by the inventors. The court noted, "[R]eal world considerations provide a colorful picture of the state of the art, what was known by those in the art, and a solid evidentiary foundation upon which to rest a nonobviousness determination." *Id.* at 1575.

In the present case, the Appellants have provided evidence of incremental developments in protein formulation science, particularly as it relates to FSH. These data were

provided via the Declaration of Dr. John M. Beals, submitted February 18, 2003. The declaration establishes the recognized instability of FSH. Quoting Skrabanja, Dr. Beals notes that gonadotropins (*e.g.*, FSH) in aqueous solution are insufficient for long-term storage and thus is usually stored as a lyophilized powder (*see* paragraph 70). He notes the efforts of inventors such as Samaritani and Boime to stabilize "time-unstable" highly purified proteins by adding saccharides and amino acids or strengthening the chemical bonds (*see* paragraph 71). Like the incremental steps of the inventors in *Minnesota Mining*, *supra*, the prior art efforts to find a stable solution formulation of FSH, described by Dr. Beals, establish the need for a stable FSH solution formulation (*see* paragraphs 41, 68 and 72 through 77).

Dr. Beals's declaration describes FSH products for use in humans that were available for sale over the thirty years prior to the claimed invention (*see* paragraphs 8-41). Six products were marketed, none of which contained an antimicrobial preservative. Each product was provided in single-dose vials or cartridges, despite the dosing regimen that required multiple injections (typically 1–3 injections per day), over a period of 10-14 days. Dr. Beals notes that "one skilled in the art would naturally have been strongly motivated for more than thirty years to develop, if possible, a multi-dose preserved product." *See* paragraph 72.

Dr. Beals further notes that another gonadotropin, namely hCG, had been formulated for use as a solution preserved with benzyl alcohol since at least as early as 1965 (*see* paragraph 46). Seven products are described, at least four of which were preserved with benzyl alcohol (*see* paragraphs 42-59). Furthermore, Dr. Beals describes at least eight other proteins that contained an antimicrobial preservative (*see* paragraphs 60-68). Thus, the means to create a multi-dose product that was usable over an extended period of time, such as 10-14 days, were generally known (*see* paragraph 57). Yet, a multi-dose FSH solution, preserved with benzyl alcohol and suitable for administration by injection, was never disclosed, produced, or marketed over a period of more than thirty years. This is all the more astonishing for the fact that, whereas there is little or no motivation to provide hCG as a multi-dose product because the overwhelmingly greatest use of that product does not require administering multiple doses, there was for the entire thirty or so years a continuing, strong motivation to discover and provide to patients a multi-dose FSH product because FSH is always given multiple times during a course of therapy! The fact that the present invention was needed far more than the known, preserved, multi-dose hCG products for more than thirty years is **powerful, contemporaneous evidence of**

non-obviousness, which has not been considered or refuted by the Examiner.

E. Evidence of Surprising or Unexpected Results

The ordinarily skilled formulation scientist, knowing of the instability associated with aqueous protein solutions and that FSH products were consistently marketed only as lyophilized products for over thirty years, would not have anticipated the level of conformational stability that was achieved in the instant invention. *See* Beals, paragraphs 41, 68 and 72. FSH is a non-covalently bonded heterodimer; it consists of two subunits, α and β, weakly associated by hydrophobic and electrostatic interactions, hydrogen bonding, and van der Waals forces. Because non-covalent bonds are relatively weak, they are more easily disrupted than covalent bonds. Conformational stability is the ability for the heterodimer to maintain association between the subunits, thereby maintaining biological activity.

It was known that very pure FSH was conformationally unstable. *See, inter alia,* Skrabanja, p. 3, lines 51-54. Relatively dilute aqueous solutions were known to be particularly unstable. *Id.* In light of its instability, FSH was often stored as a lyophilized powder to be reconstituted with solvent immediately before use.

Furthermore, the addition of preservatives to protein solutions was known to cause degradation of the protein in some situations. *See, e.g.*, degradation of human growth hormone, Maa and Hsu, *Intl. J. Pharm.* 140:155-58 (1996), Appellants' IDS reference CBU; degradation of human interferon-gamma, Lam *et al.*, *Pharm. Res.* 14(6):725-29 (1997), reference CAC; degradation of interleukin-1 receptor, Remmele *et al.*, *Pharm. Res.* 15(2):200-08 (1998), reference CAA; and degradation of human insulin-like growth factor I, Fransson *et al.*, *Pharm. Res.* 14(5):606-12 (1997), reference CAB.

Conformational and physical stability of one protein cannot be predicted from the successes and failures of others. However, knowing the instability of FSH and the destabilizing effects of preservatives on some proteins, the person of ordinary skill in the art would not have expected a stable formulation of FSH and benzyl alcohol. Nonetheless, in the preserved formulation of the instant invention, the FSH heterodimer exhibits comparable physical and conformational stability to an unpreserved control FSH solution that lacks benzyl alcohol. *See* the '198 Application, Examples 9 and 13. Such results were surprising to the Appellants, who had relied on thirty years of general knowledge that FSH was always supplied as a lyophilized

powder. Additionally, these results were surprising considering the statement by Donaldson, *supra*, teaching away from the use of benzyl alcohol with FSH ("Of the 24 antimicrobial preservatives listed on Page 1491 of U.S.P. XXI, and U.S.P. and NF Pharmaceutical Ingredients, Thymol (5-methyl-2(1-methylethyl) phenol) was found to be compatible with FSH." Donaldson, col. 25, lines 63-67. As benzyl alcohol is one "of the 24" preservatives listed, results of the conformational stability of FSH with benzyl alcohol are indicative of the non-obviousness of the invention.

Again, the Examiner fails to refute the evidence provided by the Appellants. She provides no evidence to explain why a person of ordinary skill in the art would add a known destabilizing agent (benzyl alcohol) to FSH when the art teaches away from doing so.

F. Evidence of Commercial Success

For a showing of commercial success, "the record must show a sufficient nexus between this commercial success and the patented invention." *Gambro Lundia AB v. Baxter Healthcare Corp.*, 110 F.3d 1573, 1579, 42 U.S.P.Q.2d 1378, 1384 (Fed. Cir. 1997). Since the effective date of filing the instant invention, two multi-dose FSH products, preserved with benzyl alcohol, have been launched: PUREGON® brand FSH and GONAL-F® MULTI-DOSE brand FSH. One product, Gonal-F, was listed in the Petition to Make Special under 37 CFR § 1.102(d) – Statement Alleging Infringement, filed in present case on August 10, 2001. Both products comprise human FSH and a preservative in an aqueous diluent, wherein (a) the preservative is benzyl alcohol, (b) the concentration of FSH is 5.0 μg/mL to 2 mg/mL, (c) the FSH consists of an α-subunit having SEQ ID NO:5 and a β-subunit having SEQ ID NO:6, held together by noncovalent interactions, and (d) the formulation is suitable for multi-dose administration by injection.

Within two years of their introduction, GONAL-F® MULTI-DOSE brand FSH has garnered 15.7% of the US market, 25.2% of the Canadian market and 18.8% of the European market. PUREGON® has garnered 24.2% of the Canadian market and 23.9% of the Europe market (The US product, Follistim®-AQ, was approved in 2004, and thus, US data are not available).

A review of Serono's website (http://www.seronofertility.com/to_ht_gonalF.jsp) makes clear that the success of GONAL-F® MULTI-DOSE is attributable to the use of benzyl

alcohol thereby making the reconstituted formulation suitable for multi-dose administration. For example, the website provides:

> Gonal-f® is the most prescribed FSH in the US and in the world. It is the only FSH available in convenient multi-dose vials, offering several important benefits to patients:
>
> **Fewer Steps** Gonal-f® Multi-Dose comes with a pre-filled diluent syringe, eliminating the extra step of preparing a diluent syringe.
>
> **Less Mixing** Each Gonal-f® Multi-Dose vial contains as much medicine as 14 single dose vials or ampules of 75 IU each, so you only have to mix one time to have treatment prepared over several days. After reconstitution, the solution must be refrigerated.
>
> Patient-Preferred
> In a recent study, 96% of patients said Gonal-f® Multi-Dose was easy to handle, and 94% preferred the convenience of one-step reconstitution.[1]...
>
> [1] Hinrichsen MJ, Weise G. German Phase III open multicenter study to evaluate the convenience and safety of recombinant FSH injections supplied as 1200 IU multidose (Gonal-f® Multi-Dose) in ART cycles. ESHRE, June 2002.

With regard to PUREGON®, which is now approved in the US as FOLLISTIM®, Organon, the manufacturer, stated:

> The U.S. Food and Drug Administration (FDA) today announced approval of Follistim®-AQ TM cartridge (follitropin beta injection) in the United States. Follistim-AQ cartridge is the first follicle stimulating hormone (FSH) treatment available in a pre-filled, pre-mixed solution, eliminating the need for patients to mix one or more vials of medication. . . . Follistim-AQ cartridge, used with the Follistim Pen, provides women with a discreet, convenient method to self-administer fertility treatment with ease and confidence using the unique dial-a-dose feature. Organon USA Inc. markets Follistim-AQ cartridge and Follistim Pen. In Europe it is marketed under the brand name PUREGON Pen®.

24 March 2004 *(Arnhem, The Netherlands).* Although not explicit in the press release, Follistim-AQ is a solution comprising FSH and benzyl alcohol so that the solution can be used over the course of therapy.

The commercial success of these products provides further evidence that the present invention provided a significant and nonobvious advance over the art and is therefore patentable.

G. Conclusion

In summary, the rejection of Claim 128 as unpatentable over Keene in view of Skrabanja and Andya is inappropriate. Looking at all the factors required by *Graham*, it is evident that the instant invention is not obvious. Review of the prior art and knowledge generally available indicates that a person of ordinary skill in the art would not have expected a dilute, FSH solution to maintain conformational stability, especially if a preservative such as benzyl alcohol were added. The stability achieved with the instant invention was therefore quite unexpected. Furthermore, the invention fulfilled a thirty-year, long-felt but unresolved need. This fulfillment is particularly demonstrated by the rapid commercial success achieved by two commercial products comprising FSH and benzyl alcohol. This evidence compels a finding of non-obviousness in the instant case.

Although objective evidence has been provided throughout the prosecution of the patent application, the Examiner has continually failed to consider, let alone refute or rebut the evidence. Instead, she has summarily rejected pending claims without addressing the evidence. This is not in accordance with the requirements for establishing a rejection for obviousness under 35 U.S.C. § 103(a).

III. THE INVENTION DOES NOT CONSTITUTE OBVIOUSNESS-TYPE DOUBLE PATENTING BECAUSE THE APPELLANTS HAVE OFFERED TO FILE A TERMINAL DISCLAIMER.

The Examiner has provisionally rejected Claim 128 under the judicially created doctrine of double patenting over Claims 159 and 160 of copending application 09/744,431 in view of Keene, Skrabanja, and Andya, *supra*. The Examiner states that although the claims are not identical, but they are not patentably distinct.

According to the M.P.E.P.:

> A rejection based on a nonstatutory type of double patenting can be avoided by filing a terminal disclaimer in the application or proceeding in which the rejection is made. *In re Vogel*, 422 F.2d 438, 164 U.S.P.Q. 619 (C.C.P.A. 1970); *In re Knohl*, 386 F.2d 476, 155 U.S.P.Q. 586 (C.C.P.A. 1967); and *In re Griswold*, 365 F.2d 834, 150 U.S.P.Q. 804 (C.C.P.A. 1966).

M.P.E.P. § 804.02. In the present case, the Appellants offered to file a terminal disclaimer on October 16, 2003. The rejection should have been held in abeyance pending resolution of this appeal. However, because the rejection was stated in the final rejection, Appellants will file a terminal disclaimer upon allowance of Claim 128, thereby obviating the obviousness-type double patenting rejection.

Summary

For all of the foregoing reasons, the Appellants submit that the Examiner's rejections of Claim 128, under 35 U.S.C. § 103(a) and obviousness-type double patenting, were in error and should be reversed. Appellants respectfully request reversal of the present rejections and passage of the present case to issuance.

Respectfully submitted,

Paula K Davis

Paula K. Davis
Attorney for Appellants
Registration No. 47,517

Phone: 317-433-3422

Eli Lilly and Company
Patent Division
P.O. Box 6288
Indianapolis, Indiana 46206-6288

Sept. 20, 2004

Claims Appendix

Claims at issue in this appeal.

Claim 128 (new): A pharmaceutically acceptable, solution formulation comprising human FSH and benzyl alcohol in an aqueous diluent, wherein

(a) the concentration of FSH is 5.0 μg/mL to 2 mg/mL,

(b) the FSH consists of an α-subunit having SEQ ID NO:5 and a β-subunit having SEQ ID NO:6, held together by noncovalent interactions, and

(c) the formulation is suitable for multi-dose administration by injection.

Evidence Appendix

I. Declaration of Dr. John Beals, submitted February 18, 2003.

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	James A. Hoffmann & Jirong Lu	
Serial No.	:	09/928,198	Group Art Unit: 1646
Filed	:	August 10, 2001	
For	:	FSH Formulation	Examiner: R. DeBerry
Docket No.	:	X-12383N	

DECLARATION UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Arlington, VA 22202
Sir:

I, John M Beals, declare that:

1. I hold the degree of Ph.D. in Biochemistry from the University of Notre Dame, Notre Dame, Indiana (1987).

2. I have been employed since 1990 by Eli Lilly and Company in the following capacities: Sep, 1990 to Oct, 1994: Senior Pharmaceutical Chemist; Oct, 1994 to Jan, 1999: Research Scientist; Jan, 1999 – present: Senior Research Scientist, Group Leader. In these positions, I have been responsible for, among other things, research on protein-excipient interactions in formulations and their influence on protein formulation stability, structural properties of proteins for NDA submission, pre-formulation characterization of a new protein drug candidate, and technical direction of research efforts on internal bioproduct opportunities

associated with diabetes, inflammation, cardiovascular disease, dementia, autoimmune disease, and hematopoiesis.

3. I have authored or co-authored twenty-six (26) publications in reviewed journals.

4. I am the inventor or co-inventor of several pending United States patent applications, and no issued US patents.

5. I am not an inventor named in this application.

6. I have reviewed the application and the Office Action.

7. My Curriculum vitae is attached.

FSH PRODUCTS

I further declare that:

8. At the time that the presently claimed invention was made, none of the following FSH products contained a preservative, let alone benzyl alcohol. I am not aware of the composition of any other FSH product at the time that the invention was made.

Pergonal

9. From at least as early as 1975, Serono marketed an FSH product, called Pergonal, which contained "a purified preparation of gonadotropins extracted from the urine of postmenopausal women."[1] Pergonal was supplied as an ampoule that contained 75 IU of FSH and 75 IU of LH plus lactose in a lyophilized form.[2] To administer the product, the user was instructed to "[d]issolve the contents of one ampule of Pergonal in one to two ml. of sterile saline and administer intramuscularly immediately." Any unused reconstituted material was to be discarded.[3]

---

1 Physician's Desk Reference ("PDR"), 29th Ed., 1975, pages 1366 – 1367 (Reference CAS).

2 Reference CAS, PDR 29th Ed., page 1367.

3 Id.

10. Three other PDR excerpts likewise indicate that Pergonal contained a mixture of FSH and LH, that the lyophilized material was to be reconstituted with a saline diluent, then used immediately, and any remaining discarded.[4] None of the cited PDR excerpts mention that Pergonal contained a preservative, but they all clearly indicate that Pergonal was a single-use product.

11. Pergonal was an FSH product that did not contain a preservative from the time of its launch in the 1960s until the time that the present invention was made.

12. Pergonal was a single-use product that needed to be reconstituted each time it was to be used.

13. Dosing with Pergonal occurred daily for between seven (or nine) and twelve days, followed by a dose of human chorionic gonadotropin (hCG),[5] which is also a heterodimeric gonadotropin.

14. As mentioned elsewhere herein, most if not all hCG products on the market at the same time as Pergonal contained a preservative (usually benzyl alcohol) and were multi-dose products.

15. Even though the recommended course of therapy with Pergonal required multiple dosings over a period of from seven to twelve days, and even though Serono, the company that manufactured and marketed Pergonal, also manufactured and marketed an hCG product (Profasi) in a preserved multi-dose form during most of the period that Pergonal was on the market, Serono never provided Pergonal as a multi-dose product.

Humegon

16. Organon marketed an FSH product, called Humegon, beginning in about 1983. Like Serono's Pergonal, Humegon was a purified preparation of gonadotropins extracted from the urine of postmenopausal females that contained both FSH and LH activity.[6] Each vial of Humegon contained either 75 or 150 IU of FSH activity and 75 or 150 IU of LH activity, plus

---

4 PDR, 49th Ed., 1995, pages 2325 – 2327 (Reference CAT); PDR, 51st Ed., 1997, pages 2618 – 2620 (Reference CAU); and PDR, 54th Ed., 2000, pages 2946 – 2947 (Reference CAV).

5 Reference CAS, page 1367; Reference CAT, page 2327; Reference CAU, page 2620; Reference CAV, page 2947.

6 PDR, 54th Ed., 2000, pages 2095 – 2097 (Reference CAW).

lactose and phosphate salts in a sterile, lyophilized form.[7] The user was instructed to dissolve the contents of one vial of Humegon in one to two mL of sterile saline, to administer intramuscularly immediately, and to discard any unused reconstituted material.[8] Therefore, Humegon was an FSH product that did not contain a preservative from the time of launch in about 1983 until the time that the present invention was made.

17. Humegon was a single-use product that needed to be reconstituted each time it was to be used.

18. Dosing with Humegon occurred daily for between seven and twelve days, followed by a dose of human chorionic gonadotropin (hCG),[9] which is also a heterodimeric gonadotropin.

19. As mentioned elsewhere herein, most if not all hCG products on the market at the same time as Humegon contained a preservative (usually benzyl alcohol) and were multi-dose products.

20. Even though the recommended course of therapy with Humegon required multiple dosings over a period of from seven to twelve days, and even though Organon, the company that manufactured and marketed Humegon, also manufactured and marketed an hCG product (Pregnyl) in a preserved multi-dose form during most of the period that Humegon was on the market, Organon never provided Humegon as a more convenient, multi-dose product.

Metrodin

21. Serono marketed an FSH product called Metrodin beginning, I believe, in about 1984, and a related FSH product called Metrodin HP beginning, I believe, in about 1993. Metrodin was a preparation of gonadotropin extracted from the urine of postmenopausal women that contained either 75 or 150 IU of FSH activity and lactose in a sterile, lyophilized form.[10] The user was instructed to dissolve the contents of one ampule of Metrodin in one to two mL of sterile saline, to administer intramuscularly immediately, and to discard any unused

---

7 Id., page 2095.

8 Id., pages 2096 – 2097.

9 Id., page 2096.

10 PDR, 51st Ed., 1997, pages 2616 – 2618 (Reference CAX).

reconstituted material.[11] Metrodin was an FSH product that did not contain a preservative from the time of launch in about 1984 until the time that the present invention was made.

22. Metrodin was a single-use product that needed to be reconstituted each time it was to be used.

23. Dosing with Metrodin occurred daily for at least seven days using from one to four vials per day, followed by a dose of human chorionic gonadotropin (hCG),[12] which is also a heterodimeric gonadotropin.

24. As mentioned elsewhere herein, most if not all hCG products on the market at the same time as Humegon contained a preservative (usually benzyl alcohol) and were multi-dose products.

25. Even though the recommended course of therapy with Metrodin required multiple dosings over a period of from seven to twelve days, and even though Serono, the company that manufactured and marketed Metrodin, also manufactured and marketed an hCG product (Profasi) in a preserved multi-dose form during the period that Metordin was on the market, Serono never provided Pergonal as a more convenient, multi-dose product.

Fertinex

26. Serono launched a single-dose FSH product called Fertinex in the 1990s that contained a highly purified FSH extracted from the urine of post-menopausal women and lactose in sterile saline after reconstitution.[13] The administration instructions state that the reconstituted solution should be administered immediately, and that any unused reconstituted material should be discarded.[14]

27. Fertinex was a single-use product that needed to be reconstituted each time it was to be used.

---

11 Id., page 2618.

12 Id.

13 PDR, 55th Ed., 2001, pages 3020 – 3022 (Reference CAY).

14 Id., page 3022.

28. Dosing with Fertrinex occurred daily for at least seven days using from one to four (or more) vials per day, followed by a dose of human chorionic gonadotropin (hCG),[15] which is also a heterodimeric gonadotropin.

29. As mentioned elsewhere herein, most if not all hCG products on the market when Fertinex was being developed and marketed contained a preservative (usually benzyl alcohol) and were multi-dose products.

30. Even though the recommended course of therapy with Fertinex required multiple dosings over many days, and even though Serono, the company that manufactured and marketed Fertinex, also manufactured and marketed an hCG product (Profasi) in a preserved multi-dose form during the period that Fertinex was being developed and marketed, Serono never provided Fertinex as a more convenient, multi-dose product prior to the present invention.

Gonal – F

31. Serono marketed an FSH product called Gonal-F beginning in about 1996. Gonal-F was a human FSH preparation of recombinant DNA origin in the form of a sterile, lyophilized powder containing r-FSH, sucrose, and phosphate salts.[16] The user was instructed to dissolve the contents of an ampule of Gonal-F in Sterile Water for Injection, U.S.P., to administer subcutaneously immediately, and to discard any unused reconstituted material.[17] Gonal-F was an FSH product that did not contain a preservative from the time of launch in about 1996 until the time that the present invention was made.

32. Gonal-F was a single-use product that needed to be reconstituted each time it was to be used.

33. Dosing with Gonal-F occurred daily for at least seven days using from one to four (or more) vials per day, followed by a dose of human chorionic gonadotropin (hCG),[18] which is also a heterodimeric gonadotropin.

---

15 Id.

16 PDR, 54th Ed., 2000, pages 2943 – 2946 (Reference CAZ).

17 Id., page 2945.

18 Id.

34. As mentioned elsewhere herein, most if not all hCG products on the market when Gonal-F was being developed and marketed contained a preservative (usually benzyl alcohol) and were multi-dose products.

35. Even though the recommended course of therapy with Gonal-F required multiple dosings over many days, and even though Serono, the company that manufactured and marketed Gonal-F, also manufactured and marketed an hCG product (Profasi) in a preserved multi-dose form during the period that Gonal-F was being developed and marketed, Serono never provided Gonal-F as a more convenient, multi-dose product prior to the present invention.

Follistim

36. Organon marketed an FSH product called Follistim beginning in about 1997. Follistim contained hFSH manufactured by recombinant DNA technology that was presented as a sterile, freeze-dried cake containing FSH, sucrose, sodium citrate, and polysorbate 20.[19] The user was instructed to dissolve the freeze-dried cake using Sterile Water for Injection, U.S.P., to administer the reconstituted Follistim immediately, and to discard any unused reconstituted material.[20] Follistim was an FSH product that did not contain a preservative from the time of launch until the time that the present invention was made.

37. Follistim was a single-use product that needed to be reconstituted each time it was to be used.

38. Dosing with Follistim occurred daily for up to 14 days, followed by a dose of human chorionic gonadotropin (hCG),[21] which is also a heterodimeric gonadotropin.

39. As mentioned elsewhere herein, most if not all hCG products on the market when Follistim was being developed and marketed contained a preservative (usually benzyl alcohol) and were multi-dose products.

40. Even though the recommended course of therapy with Follistim required multiple dosings over a period of up to 14 days, and even though Organon, the company that manufactured

---

19 PDR, 54th Ed., 2000, pages 2092 – 2095 (Reference CBA).

20 Id., page 2094.

21 Id., page 2095.

and marketed Follistim, also manufactured and marketed an hCG product (Pregnyl) in a preserved multi-dose form during most of the period that Follistim was being developed and marketed, Organon never provided Follistim as a more convenient, multi-dose product before the present invention.

Summary – FSH Products

41. Many FSH products were on the market or were introduced over a period of more than thirty years prior to the present invention. None of these products were multi-dose products, and none contained a preservative, despite the fact that all were intended to be administered multiple times to each patient who received them.

hCG PRODUCTS

I further declare that:

42. In sharp contrast, preservatives had been used in products containing a protein that is related structurally to FSH, namely, chorionic gonadotropin (CG or hCG). Like FSH, chorionic gonadotropin is comprised of an α-subunit and a β-subunit. Human FSH and human chorionic gonadotropin are comprised of the same α-subunit. The two proteins differ markedly; notably, in the amino acid sequences of their β-subunits and hCG has a C-terminal extension that FSH lacks. HCG's C-terminal extension contains several O-linked glycosylation sites.

43. At the time that the presently claimed invention was made, each of the following hCG products had contained benzyl alcohol as a preservative for many years, as many as about 35 years in one case.

A.P.L.

44. Ayerst first marketed APL in the 1950s.[22] In 1965, APL was provided in both solution form and in dry form.[23] The solution product contained chorionic gonadotropin, sodium chloride

[22] PDR, 12th Ed., 1957, page 625 (Reference CBB).

[23] PDR, 19th Ed., 1965, page 527 (Reference CBC).

and 0.5% phenol. In the dry form, chorionic gonadotropin was to be reconstituted with a sterile diluent resulting in a solution that also contained 2.0% benzyl alcohol and lactose.[24] APL was for intramuscular injection only.

45. In 1997, APL contained hCG, lactose, 2.0% benzyl alcohol, and not more than 0.2% phenol, once reconstituted.[25] APL could be stored for 30 days in a refrigerated after being reconstituted.

46. APL was an hCG product that contained benzyl alcohol from at least as early as 1965 until the time that the present invention was made.

Profasi

47. Serono began to market an hCG product, called Profasi, before 1980. Serono still marketed Profasi in 1997, at which time the product still provided human chorionic gonadotropin in lyophilized multiple dose vials together with a vial of Bacteriostatic Water for Injection containing 0.9% benzyl alcohol.[26] The 1997 PDR states that after reconstititing, Profasi needed to be refrigerated, and had to be used completely within 30 days.[27]

48. Profasi was an hCG product that contained benzyl alcohol from at least as early as 1980 until the time that the present invention was made.

Pregnyl

49. Organon marketed an hCG product, called Pregnyl, from before 1985.[28] When the freeze-dried hCG was reconstituted with Bactiostatic Water for Injection which was provided as a diluent, the resulting solution contained hCG, mannitol, phosphate salts, and 0.9% benzyl alcohol.[29] After reconstituting, Pregnyl was to be refrigerated and used within 60 days.[30]

---

24 Id.

25 PDR, 51st Ed., 1997, page 2805 (Reference CAO).

26 PDR, 51st Ed., 1997, pages 2620 – 2621 (Reference CAQ).

27 Id., page 2621.

28 PDR, 39th Ed., 1985, page 1450 (Reference CBE).

29 Id.

50. In 1997, Organon still marketed Pregnyl.[31] When reconstituted, Pregnyl contained hCG, phosphate salts, sodium chloride, and 0.9% benzyl alcohol.[32] After reconstituting, Pregnyl was to be refrigerated and used within 60 days.[33] The PDR also states that the "RECONSTITUTED SOLUTION IS STABLE FOR 60 DAYS WHEN REFRIGERATED" and "[r]econstituted material will remain stable for 60 days when refrigerated."[34]

51. Pregnyl was an hCG product that contained benzyl alcohol from at least as early as 1985 until the time that the present invention was made.

Other hCG Products

52. Several other hCG products had been on the market, including Progon, Stemutrolin, Glukor, and Follutein.

53. The administration and dosing instructions for Progon required administration of 125 to 500 IU per injection, and the product was provided in vials containing either 5,000 IU or 10,000 IU of hCG.[35] While it is not certain that Progon contained a preservative, the product was probably a multi-dose product that contained a preservative.

54. Glukor was supplied in vials of 10 cc and 25 cc, whereas, 1 cc was to be administered once or twice a week.[36] While it is not certain that Glukor contained a preservative, the product was probably a multi-dose product that contained a preservative.

55. Stemutrolin was a multiple dose product that contained hCG, urea, phosphate salts, and 1.5% benzyl alcohol after reconstitution with a diluent.[37]

---

30 Id.

31 PDR, 51st Ed., 1997, page 1878 (Reference CAP).

32 Id.

33 Id.

34 Id.

35 PDR, 19th Ed., 1965, page 646 (Reference CBF).

36 PDR, 19th Ed., 1965, page 844 (Reference CBG).

37 PDR, 24th Ed., 1970, page 867 (Reference CBH).

56. Follutein was a multiple dose product that contained hCG, sodium chloride and 0.5% phenol as a preservative after reconstitution with a sterile aqueous diluent.[38] Once reconstituted, Follutein was supposed to be stored in a refrigerator, and when refrigerated, "the solution retains its potency for 2 months, thereafter potency slowly diminishes."[39]

Summary – hCG Products

57. For more than 40 years before the present invention was made, hCG products were multi-dose products that were preserved. The most frequently used preservative was benzyl alcohol.

58. During this lengthy period in which most hCG products contained a preservative, all human FSH products were NOT preserved.

59. All the FSH products marketed in this period by the two companies that also marketed hCG products were NOT preserved.

OTHER PROTEIN PRODUCTS

I further declare:

60. During the period when FSH products were marketed as single-use products without preservatives, that is, from the 1960s through the time that the present invention was made, several other protein products were available as multi-dose products with preservatives.

Insulin and glucagon

61. Lilly and Novo marketed numerous, multi-dose formulations of insulin and glucagons, most often preserved with phenol and/or m-cresol.[40]

---

38 PDR, 24th Ed. 1970, pages 1249 –1250 (Reference CBI).

39 Id., page 1250.

40 PDR, 19th Ed., 1965, page 703 – 704, 704 - Glucagon (Reference CBJ) and page 705 – Regular Iletin (Reference CBK).

Growth Hormone

62. Serono marketed a multi-dose, growth hormone product in the 1980s called Asellacrin that could be reconstituted from a lyophilized powder using Bacteriostatic Water for Injection.[41] Bacteriostatic Water for Injection contained a preservative, though the specific preserverative was not specified.

63. Lilly launched a multi-dose, growth hormone product in about 1986 called Humatrope that contained somatropin, mannitol, glycine, phosphate salts, glycerin, and 0.3% m-cresol after reconstitution.[42] After reconstituting, Humatrope needed to be stored refrigerated (2 °C – 8 °C), and used within 14 days.[43] Humatrope was on the market when the present invention was made.

64. Genentech launched a multi-dose growth hormone product in the mid-1980s called Protropin that contained somatrem, mannitol, phosphate salts, and 0.9% benzyl alcohol after reconstitution.[44] After reconstituting, Protropin needed to be stored refrigerated (2 °C – 8 °C), and used within 14 days.[45]

65. Serono launched a multi-dose growth hormone product in about 1990 called Saizen that contained somatropin, sucrose, phosphoric acid, and 0.9% benzyl alcohol after reconstitution.[46] The reconstituted solution was supposed to be stored refrigerated (2 °C – 8 °C) for up to 14 days.[47]

---

41 PDR, 34th Ed., 1980, pages 1605 – 1606 (Reference CBL) and PDR, 39th Ed., 1985, pages 1940 – 1941 (Reference CBM).

42 PDR, 44th Ed., 1990, pages 1216 – 1217 (Reference CBN).

43 Id.

44 PDR, 44th Ed., 1990, pages 1002 – 1003 (Reference CBO).

45 Id.

46 PDR, 52nd Ed., 1998, page 2776 – 2777 (Reference CBP).

47 Id, page 2777.

Erythropoietin products

66. Amgen launched a multi-dose, erythropoietin product called Epogen in about 1990 that contained epotein alfa, albumin, sodium citrate, sodium chloride, citric acid and 1% benzyl alcohol as preservative in Water for Injection.[48] The multi-dose solution was supposed to be stored refrigerated (2 °C – 8 °C), and used within 21 days after first entry of the vial.[49]

67. Ortho Biotech launched a multi-dose erythropoietin product called Procrit in about 1990 that contained epotein alfa, albumin, sodium citrate, sodium chloride, citric acid and 1% benzyl alcohol as preservative in Water for Injection.[50] The multi-dose solution was supposed to be stored refrigerated (2 °C – 8 °C), and used within 21 days after first entry of the vial.[51]

Conclusions – Other protein products

68. During the approximately thirty year period in which all FSH products were unpreserved, single-dose products, many other protein products were provided as multi-dose products containing preservatives, including benzyl alcohol.

I further declare that:

69. The fact that all of the FSH formulations discussed above were provided in lyophilized form for reconstitution immediately before use strongly suggested either that FSH was unstable in solution or that it could not be stably formulated with a preservative.

70. The Skrabanja patent[52] states that ". . . the stability of aqueous solutions of the gonadotropins is insufficient to allow storage for longer times. This is especially true for preparations containing the very pure gonadotropins, prepared using recombinant DNA methods, in

---

48 PDR, 51st Ed., 1997, pages 489 – 494, 489 (Reference CBQ).

49 Id., page 493.

50 PDR, 51st Ed., 1997, page 1896 (Reference CBR).

51 Id.

52 U.S. Patent No. 5,929,028, col. 2, ll. 21-30 (Reference AD).

relatively dilute solutions. Usually therefore those preparations are stored in a dry form, as is obtained after lyophilization." This statement strengthens the previous conclusion that the art strongly suggested that FSH was unstable in solution or that it could not be stably formulated with a preservative.

71. Attempts to stabilize FSH in solution have been published, such as Samaratini ("It is known that highly purified proteins are time-unstable and are stabilized, for instance, in admixture with saccharides, such as lactose and mannitol or else with proteins and amino acids, such as albumin and glycine.")[53] and Biome ("The single-chain forms of the heterodimers or homodimers have a number of advantages over their dimeric forms. . . . [T]hey are generally more stable.")[54] References such as these demonstrate the instability of FSH, especially in solution formulations, and the extent to which scientists had previously attempted to resolve the instability problem.

72. Considering that FSH had to be administered once or even twice a day over a period of up to 14 days, one skilled in the art would naturally have been strongly motivated for more than thirty years to develop, if possible, a multi-dose preserved product. Such a product would eliminate product waste and patient error in mixing, and increase patient safety and convenience. The fact that this long-standing problem was not solved earlier clearly suggests that combining benzyl alcohol and FSH would have presented issues preventing the development of a multi-use formulation, indicating that such a combination was not obviously going to be successful.

CONCLUSIONS

73. Looking backward from 1998 to the time when FSH products became available for use in humans in the 1960s, FSH products sharply contrast with many other injectable protein products that had to be administered multiple times in the course of treatment.

---

53 U.S. Patent No. 5,650,390, col. 1, ll. 19-22 (Reference AF).

54 U.S. Patent No. 6,238,890, col. 4, ll. 18-20 (Reference AR).

74. From the time that FSH products for humans were first launched in the 1960s, a patient receiving FSH needed multiple injections of the product over a period of several days, up to 2 weeks. Yet, no FSH product was suitable for use as a multi-dose product because none contained a preservative. This establishes a long-standing unsatisfied need for a preserved, multi-dose product.

75. Surprisingly, the same companies that made FSH products also made multi-dose, preserved hCG products. HCG is also a heterodimeric hormone containing an alpha subunit and a beta subunit. In addition, many other preserved, multi-dose protein products were available during the more than thirty years that FSH products were uniformly unpreserved, single-dose products.

76. Looking at the long-standing need for a multi-dose FSH product and the coincident, prolonged availability of preserved, multi-dose hCG products and other protein products, a person skilled in protein formulation would have quite reasonably concluded that FSH was not be stable enough in the presence of preservatives to be a multi-dose product.

77. Based on the fact that: 1) there was a long-standing need for preserved FSH formulations for multi-dose use; 2) FSH had only been provided in lyophilized forms and had been suspected, reasonably, of being unstable in solution; and 3) despite the coincident and prolonged availability of preserved multi-dose hCG and other protein products, no one had published, used in public, or sold multi-dose, preserved, pharmaceutically acceptable formulations of FSH, I conclude that one skilled in the art was not motivated to combine the references cited by the Examiner and would not consider preserved formulations of FSH and benzyl alcohol to be obvious.

I further declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both (18 U.S.C. 1001), and may jeopardize the validity of the application or any patent issuing thereon.

Application No. 09/928,198
Appeal brief dated Sept. 20, 2004
Evidence Appendix: Declaration of Dr. John Beals

John M. Beals, Ph.D.

February 18, 2003

Curriculum Vitae

John M. Beals, Ph.D.

Business
Lilly Research Laboratories
Eli Lilly and Company
Lilly Corporate Center
DC 1505
Indianapolis, IN 46285
Phone: (317) 276-1682
FAX: (317) 277-8200
Email: Beals_John_M@lilly.com

Home
6710 Bluffridge Parkway
Indianapolis, IN 46278-1853
Phone: (317) 291-8172
Email: Beals_John_M@msn.com

Tuesday, January 28, 2003

EDUCATIONAL RECORD:

8/1977 to 5/1981	Loras College, Dubuque, Iowa B.S. Degrees in Biology and Chemistry GPA: 3.706, Magna Cum Laude Advisors: Dr. Edward T. Cawley and Dr. Kenneth Kraus Thesis: *"Water quality of the* Catfish Creek watershed, 1980; *An overview."*
8/1981 to 5/1987	University of Notre Dame, Notre Dame, Indiana Ph.D. Degree in Chemistry Field: Biochemistry GPA: 3.500 Advisor: Dr. Francis J. Castellino Thesis: *"I: Evaluation of the phosphatidylserine requirement of the intrinsic Factor X activating system. II. Homology and secondary structure in serine proteases."*

EXPERIENCE:

1979 Summer	Participant in the University of Illinois' Undergraduate Research Program in Engineering, Champaign, IL. *Program provided independent research in the area of fiber reinforced concrete.*
1980 Summer	Student Director of the 1980 Student-Oriented Studies Program, Loras College. *Responsibilities included management of scientific research team and financial resources.*

8/1981 to 8/1982	Teaching Assistant, University of Notre Dame. *Responsibilities included instruction and supervision of under-graduate chemistry laboratories, administration and grading of examinations and laboratory reports.*
8/1983 to 4/1987	Research Assistant, University of Notre Dame. *Research focused on the intrinsic Factor X activating system in the bovine coagulation system.*
4/1987 to 7/1990	National Institute of Health Postdoctoral Fellow Cornell University, Ithaca, New York Field: Biophysical Chemistry Advisor: Dr. Harold A. Scheraga *Research focused on protein folding in bovine RNase A.*
9/1990 to 10/1994	Senior Pharmaceutical Chemist Eli Lilly and Company, Indianapolis, Indiana Parenteral Products Research and Development *Research has focused on protein-protein and protein-excipient interactions as well as manufacturing process unit operations investigations to determine their influence on protein formulations.*
10/1994 to 6/1997	Research Scientist Eli Lilly and Company, Indianapolis, Indiana Biopharmaceutical Product Development *Research has focused on protein-protein and protein-excipient interactions in formulations for marketed product support, manufacturing process unit operations and their influence on protein formulation stability for marketed product support, structural properties of proteins for NDA submission, and pre-formulation characterization of a new protein drug candidate.*
6/1997 to 1/1999	Research Scientist Eli Lilly and Company, Indianapolis, Indiana bioResearch Technologies and Proteins: Protein Optimization Team *Initial focus of my efforts was on the interviewing, hiring, and establishment of a world-class protein engineering team (25-members), referred to as the Protein Optimization Team. Research has focused on the rational development of a stable, new protein drug candidate for IND submission.*
1/1999 to Present	Senior Research Scientist, Group Leader Eli Lilly and Company, Indianapolis, Indiana bioResearch Technologies and Proteins: Protein Optimization Team *Technical direction of research efforts on internal bioproduct opportunities associated with diabetes, inflammation, cardiovascular disease, dementia, autoimmune disease, and hematopoiesis. Efforts focused on engineering properties into bioproducts that enhance the pharmaceutical*

attractiveness and usefulness of the bioproduct. In addition, I supported the evaluation of potential in-licensing opportunities and contributed to legal support of numerous patents.

PUBLICATIONS:

Cummings, H. S., Ploplis, V. A., Beals, J. M., and Castellino, F. J. (1984). "Interspecies cross reactivity of monoclonal antibodies to various epitopes of human plasminogen", *Arch. Biochem. Biophys. 230,* 306-315.

Duman, J. G., Neven, L. G., Beals, J. M., Olson, K. R., and Castellino, F. J. (1985). "Freeze-tolerance adaptations, including haemolymph protein and lipoprotein nucleators in the larvae of the cranefly, *Tipula trivittata*", *J. Insect. Physiol. 31,* 1-8.

Neven, L. G., Duman, J. G., Beals, J. M., and Castellino, F. J. (1986). "Overwintering adaptation of the stage beetle, *Ceruchus piceus*. removal of ice nucleators in winter to pomote supercooling", *J. Comp. Physiol. B. 156,* 707-716.

Powell, J. R., Beals, J. M., and Castellino, F. J. (1986). "Secondary predictions of human plasminogen and the bovine prothrombin kringle loops", *Arch. Biochem. Biophys. 248,* 390-400.

Castellino, F. J., Sator de Serrano, V., Powell, J. R., Johnson, W. R., and Beals, J. M. (1986). "Examination of the secondary structure of the kringle 4 domain of human plasminogen", *Arch. Biochem. Biophys. 247,* 312-320.

Beals, J. M. and Castellino, F. J. (1986). "The interaction of bovine factor IX, its activation intermediate, factor IXα, and its activation products, factor IXaα and factor IXaβ, with acidic phospholipids of varying composition", *Biochem. J. 236,* 861-869.

Castellino, F. J., Chibber, B. A. K., Beals, J. M., and de Serrano, V. S. (1987) "The structure and activation of human plasminogen", in *Fundamental and Clinical Fibrinolysis*, eds. Castellino, F. J., et al., Elsevier Science Publishers B. V. (Biomedical Division).

Beals, J. M. (1987) "I. Evaluation of the phosphatidylserine requirement of the intrinsic factor X activating system. II. Homology and secondary structure in serine proteases", Ph. D. Thesis, University of Notre Dame, Notre Dame, IN.

Castellino, F. J. and Beals, J. M. (1987). "The genetic relationships between the kringle domains of human plasminogen, prothrombin, Tissue Plasminogen Activator, Urokinase and Coagulation Factor XII", *J. Mol. Evol., 26,* 358-369.

Beals, J. M., and Castellino, F. J. (1988) "Circular dichroism analysis of the secondary structure of bovine blood coagulation factor IX, factor X, and prothrombin", *J. Protein. Chem., 7,* 593-612.

Beals, J. M., Weber, J., Derwent, P., Grant, K. L., and Castellino, F. J. (1988) " Prediction of the secondary structures of bovine blood coagulation factor IX, factor X and prothrombin", *J. Protein. Chem., 7,* 613-632.

Beals, J. M., Chibber, B. A. K., and Castellino, F. J. (1989) "The evaluation of the phosphatidylserine requirement in the factor X activating complex", *Arch. Biochem. Biophys., 268,* 485-501.

Castellino, F. J., Urano, T., deSerrano, V. S., and Beals, J. M. (1990) "The structure and activation of human plasminogen", in *Lipoprotein(a)*, Chapter 6, 87-101, Academic Press, Inc.

Beals, J. M., Haas, E., and Scheraga, H. A. (1991) "Conformational studies of a peptide corresponding to a region of the C-terminus of ribonuclease A: Implications as a potential chain-folding-initiation-site", *Biochemistry, 30,* 7680-7692.

Scheraga, H. A., Beals, J. M., Buckler, D. R., Haas, E., and Krausz, S. (1992) "Structure and dynamics of chain-folding-initiation-sites in ribonuclease A." in *Time-Resolved Laser Spectroscopy in Biochemistry III.* Ed. J. Lackowicz. Bellingham, WA: Society of Photo-Optical Instrumentation Engineers, 1640: 672-675.

Hardaway, L. A., Brems, D. N., Beals, J. M., and McKenzie, N. E. (1994) "Amide hydrogen exchange of the central B-chain helix within the T & R states of insulin hexamers", *Biochim. Biophys. Acta 1208,* 101-103.

Dodd, S. W., Havel, H. A., Kovach, P. M., Lakshminarayen, C., Redmon, M. P., Sargeant, C. M., Sullivan, G. R., and Beals, J. M. (1995) "Reversible adsorption of soluble hexameric insulin onto the surface of insulin crystals cocrystallized with protamine: An electrostatic interaction", *Pharmaceutical Research 12,* 60-68.

Ciszak, E., Beals, J. M., Frank, B. H., Baker, J. C., Carter, N. D., and Smith, G. D. (1995) "Role of C–terminal B–chain residues in insulin assembly: The structure of hexameric $Lys^{B28}Pro^{B29}$-human insulin", *Structure 3,* 615-622.

Birnbaum, D. T., Dodd, S. W., Saxberg, B. E. H., Varshavsky, A. D., and Beals, J. M. (1996) "Hierarchical modeling of phenolic ligand binding in 2Zn–insulin hexamers", *Biochemistry 35,* 5366-5378.

Bakaysa, D. L., Beals, J. M., Brader, M. L., Dodd, S. W., Edwards, S. L., Havel, H. A., Radziuk, J., and Brems, D. N. (1996) "Physicochemical basis for the rapid time-action of $Lys^{B28}Pro^{B29}$-insulin: Dissociation of a protein-ligand complex", *Protein Science 5,* 2521-2531.

Birnbaum, D. T., Kilcomons, M. A., DeFelippis, M. R., and Beals, J. M. (1997) "Hexameric kinetics of association and dissociation of a fast acting insulin analog: $Lys^{B28}Pro^{B29}$-insulin", *Pharmaceutical Research 14,* 25-36.

Beals, J. M. and Kovach, P. M. (1997) "Insulin", Chapter 10 in *Pharmaceutical Biotechnology for Pharmacists and Pharmaceutical Scientists,* Eds. D. J. A. Crommelin and R. D. Sindelar. Harwood Academic Publishers gmbh, Amsterdam, pp. 229-239.

Zhang, F., Basinski, M. B., Beals, J. M., Briggs, S. L., Churgay, L. M., Clawson, D. K., DiMarchi, R. D., Furman, T. C., Hale, J. E., Hsiung, H. M., Schoner, B. E., Smith, D. P., Zhang, X. Y., Wery, J.-P., Schevitz, R. W. (1997) "Crystal structure of the *obese* protein leptin-E100", *Nature* 387, 206-209.

Varshavsky, A. D., Birnbaum, D. T., Beals J. M., and Saxberg, B. E. H. (2000) "Global stochastic optimization in hierarchical modeling of ligand/protein binding profiles", *Kybernetes 29(4)*, 452-472.
Beals, J. M., Brader, M. L., DeFelippis, M. R., and Kovach, P. M. (2002) "Insulin", Chapter 10 in Pharmaceutical Biotechnology, 2nd Edition, Eds. Crommelin, D. J. A. and Sindelar, R. D. Routledge Publishers, London and Newyork, 231-244.

Darling R. J., Kuchibhotla U., Glaesner W., Micanovic R., Witcher D. R., Beals J. M. (2002) "Glycosylation of erythropoietin affects receptor binding kinetics: role of electrostatic interactions", *Biochemistry 41(49)*, 14524-31.

PRESENTATIONS:

"Interaction of bovine factor IX and its activation intermediates and products with defined membranes of varying composition", Beals, J. M. and Castellino, F. J., Meeting of the American Society of Biological Chemists, April, 1985, Anaheim, California.

"Structural homology between bovine Christmas factor and Stuart factor", Beals, J. M., Johnson, W. R., Derwent, P. F., and Castellino, F. J., Joint Meeting of the American Society of Biological Chemists and the Division of Biological Chemistry of the American Chemical Society, June, 1986, Washington, D. C.

"The role of surface charge in the assembly of coagulation factors on phospholipid vesicles", Chibber, B. A. K., Beals, J. M., and Castellino, F. J., International Symposium on Biochemical Role of Eukaryotic Cell Surface Macromolecules, January, 1987, New Delhi, India.

"Conformational studies of a peptide corresponding to a region of the C-terminus of ribonuclease A: Implications as a potential chain-folding-initiation-site", Beals, J. M., Eli Lilly and Company, January, 1990, Indianapolis, Indiana.

"Conformational studies of a peptide corresponding to a region of the C-terminus of ribonuclease A: Implications as a potential chain-folding-initiation-site", Beals, J. M., Kraft Foods, January, 1990, Glenview, Illinois.

"Conformational studies of a peptide corresponding to a region of the C-terminus of ribonuclease A: Implications as a potential chain-folding-initiation-site", Beals, J. M., University of Cincinnati, February, 1990, Cincinnati, Ohio.

"Conformational studies of a peptide corresponding to a region of the C-terminus of ribonuclease A: Implications as a potential chain-folding-initiation-site", Beals, J. M., Merck Pharmaceutical, Inc., March, 1990, Rahway, New Jersey.

"Conformational studies of a peptide corresponding to a region of the C-terminus of ribonuclease A: Implications as a potential chain-folding-initiation-site", Beals, J. M., Proctor and Gamble, March, 1990, Cincinnati, Ohio.

"Conformational studies of a peptide corresponding to a region of the C-terminus of ribonuclease A: Implications as a potential chain-folding-initiation-site", Beals, J. M., Oregon State University, April, 1990, Corvalis, Oregon.

"Conformational studies of a peptide corresponding to a region of the C-terminus of ribonuclease A: Implications as a potential chain-folding-initiation-site", Beals, J. M., Zymogenetics, Inc., April, 1990, Seattle, Washington.
"Pharmaceutical Opportunities for Biochemists", Beals, J. M., ACS Roadshow, Saginaw Valley State University, November, 1991, Saginaw, Michigan.

"Humulin R adsorption studies onto NPH crystals: An isothermal titration calorimetry study", Beals, J. M., and Dodd, S. W., Lilly Insulin Technical Conference, June 14, 1992, Fegersheim, FR.

"Adsorption of soluble insulin onto NPH insulin crystals: An electrostatic interaction", Beals, J. M., Dodd, S. W., Havel, H. A., Lakshminarayan, C., Redmon, M. P., Sargeant, C. M., Sullivan, G. R., and Kovach, P. M., Lilly Expo, Feburary, 1993, Eli Lilly & Co., Indianapolis, Indiana.

"Effects of manufacturing variables on the physical stability of Humulin® N/R mixtures in cartridges", Redmon, M. P., Crawford, D. E., Fites, A. L., Townsend, M. W., Kaczmarczyk, J–P., Sargeant, C. M., Murphy, J. R., Kovach, P. M., and Beals., J. M., Lilly Expo, Feburary, 1993, Eli Lilly & Co., Indianapolis, Indiana.

"Future insulin technology report", Hollinden, C. S., Beals, J. M., Allen, R. B., Hughes, M. T., and Smith, B. H., Internal Technology Talks, June 1993 – July 1993, Eli Lilly & Co., Indianapolis, Indiana.

"T—>R transition in 2Zn-insulin hexamer: Development of the algorithm for modeling the cooperative binding of preservative", Varshavsky, A. D., Saxberg, B. E. H., Dodd, S. W., and Beals, J. M., 48th Annual Calorimetry Conference, July, 1993, Durham, North Carolina.

"T—>R Transition in 2Zn-Insulin Hexamer: Analysis of Cooperative Preservative Binding from Isothermal Calorimetry Data", Beals, J. M., Dodd, S. W., Varshavsky, A. D., and Saxberg, B. E. H., 48th Annual Calorimetry Conference, July, 1993, Durham, North Carolina.

"Formulation Interactions in NPH Mixtures", Beals, J. M., Pharmaceutical Product Development Seminar Series, November, 1993, Eli Lilly & Co., Indianapolis, Indiana.

"NPH crystallization: The effect of [Zinc], [protamine], [Human Insulin], and pH on crystal size, crystal morphology, surface adsorption properties, and sedimentation volumes", Beals, J. M., Sullivan, G. R., and Dodd, S. W., Lilly Insulin Technical Conference, March 7, 1994, Fegersheim, FR.

"Time-dependent NPH crystallization: A particle sizing and microscopy study", Beals, J. M., and Dodd, S. W., Lilly Insulin Technical Conference, March 7, 1994, Fegersheim, FR.

"Protein-protein and protein-ligand interactions in NPH formulations", Beals, J. M., March, 1994, Loras College, Dubuque, Iowa.

"Pharmaceutical Opportunities for Biochemists", Beals, J. M., March, 1994, Loras College, Dubuque, Iowa.

"Adsorption of Soluble Insulin Hexamer onto the Surface of Insulin Crystals Cocrystallized with Protamine", Beals, J. M., Dodd, S. W., Havel, H. A., Lakshminarayan, C., Redmon, M. P., Sargeant, C. M., Sullivan, G. R., and Kovach, P. M., August, 1994, 49th Annual Calorimetry Conference; Santa Fe, New Mexico.

"The structure of LysPro-insulin", Ciszak, E., Smith, G. D., Baker, J. C., Beals, J. M., Carter, N. D. and Frank, B. H., June, 1994, American Crystallographic Association, Atlanta, Georgia.

"Isothermal titrating calorimetry study of phenolic ligand binding in 2Zn- and 2Co- insulin hexamers in the presence of chloride ion", Beals, J. M., Birnbaum, D. T., Dodd, S. W., Varshavsky, A. D., and Saxberg, B. E. H., August, 1994, 49th Annual Calorimetry Conference; Santa Fe, New Mexico.

"Mathematical modeling and algorithms for phenolic ligand binding to insulin hexamer : Model refinement to optimize fit for reduced dimensionality", Varshavsky, A. D., Beals, J. M., and Saxberg, B. E. H., August, 1994, 49th Annual Calorimetry Conference; Santa Fe, New Mexico.

"Adsorption of soluble insulin hexamer onto the surface of insulin crystals cocrystallized with protamine", Beals, J. M., Dodd, S. W., Havel, H. A., Lakshminarayan, C., Redmon, M. P., Sargeant, C. M., Sullivan, G. R., and Kovach, P. M., October 21, 1994, Bioprocess Research and Development Seminar Series, Eli Lilly & Co., Indianapolis, Indiana.

"The Structure of Lys^{B28}-Pro^{B29}-Insulin", Frank, B. H, Baker, J. C., Beals, J. M., Carter, N. D., Ciszak, E., Pekar, A. H., and Smith, G. D., November 6, 1994, International Diabetes Federation, Kobe Japan.

"Hierarchical modeling of phenolic ligand binding in 2Zn– and 2Co–insulin hexamers: Enthalpy and entropy compensation considerations", Birnbaum, D. T., Dodd, S. W., Saxberg, B. E. H., Varshavsky, A. D., and Beals, J. M., March 21, 1995, Computational Chemistry Seminar Series, Eli Lilly & Co., Indianapolis, Indiana.

"Formation and Disruption Kinetics of Cobalt-Insulin Hexamers: Ligand/Anion Binding and Cooperativity", Birnbaum, D. T., Kilcomons, M. A., Beals, J. M., and DeFelippis, M. R., July 8-12, 1995, 9th Symposium of The Protein Society, Boston, Massachusetts.

"Crystal Structure of the obese Protein Glu^{100}hOB", Zhang, F., Basinski, M. B., Beals, J. M., Briggs, S. L., Churgay, L. M., Clawson, D. K., DiMarchi, R. D., Furman, T. C., Hale, J. E., Hsiung, H. M., Schoner, B. E., Smith, D. P., Zhang, X. Y., Wery, J.-P., Schevitz, R. W., July 19-25, 1997, American Crystallization Association Meeting, St. Louis, Missouri.

"Structural Studies of LisPro-insulins", Ciszak, E., Frank, B. H., Beals, J. M., Yip, C. M., DeFelippis, M. R., Smith, G. D., July 19-25, 1997, American Crystallization Association Meeting, St. Louis, Missouri.

"Structure and Function of LysPro–Insulin: Insights Discovered During Development and Commercialization", Beals, J. M., DeFelippis, M. R., and Frank, B. H., May 19, 1995, Grand Rounds Seminar Series, Eli Lilly & Co., Indianapolis, Indiana.

"Reversible Adsorption of Soluble Hexameric Insulin onto the surface of Insulin Crystals Cocrystallized with Protamine: An Electrostatic Interaction", Dodd, S. W., Havel, H. A., Kovach, P. M., Lakshminarayen, C., Redmon, M. P., Sargeant, C. M., Sullivan, G. R., and Beals, J. M., May 22, 1995, American Association of Pharmaceutical Scientists Midwest Regional Meeting, Chicago Illinois.

"Structure and Function of LysPro–Insulin", Beals, J. M., June 8-9, 1995, Diabetes Care Global Conference: Approaching Physiologic Control of Blood Glucose in Patients with Diabetes Mellitus, Eli Lilly & Co., Indianapolis, Indiana.

"The Development of LY355101: A Story Explored, in part, by a Protein Iteration Philosophy." Beals, J. M. and Wery, J.-P., March 1997, Grand Rounds Seminar Series, Eli Lilly & Co., Indianapolis, Indiana.

"A Researcher's View of Statistical Design of Experiments for Assessing Biophysical Properties of Biopharmaceutical Formulations", Beals, J. M., May 19-21, 1997, Midwest Biopharmaceutical Statistics Workshop, Muncie, Indiana.

"Receptor Binding Kinetics of Erythropoietin are Affected by Glycosylation: Role of Electrostatic Interactions", Darling, R. J., Kuchibhotla, U., and Beals, J. M., February 10-15, 2002, Gordon Research Conference on Reversible Associations in Structural and Molecular Biology, Ventura, California.

"Understanding the Role of Electrostatics in Erythropoietin Receptor/Ligand System", Beals, J. M., Darling, R. J., and Kuchibhotla, K., April 19, 2002, Loras College, Dubuque, Iowa.

"Scientific Career Opportunities at Lilly", Beals, J. M., April 19, 2002, Loras College, Dubuque, Iowa.

"Understanding the Role of Electrostatics in Erythropoietin Receptor/Ligand System", Beals, J. M., Darling, R. J., and Kuchibhotla, K., June 6, 2002, Keynote Talk at the University of Notre Dame Chemistry and Biochemistry Annual Retreat, Pokagon Sstate Park, Algona, Indiana.

"Scientific Career Opportunities at Lilly", Beals, J. M., June 6, 2002, University of Notre Dame Chemistry and Biochemistry Annual Retreat, Pokagon State Park, Algona, Indiana.

"Understanding the Role of Electrostatics in Erythropoietin Receptor/Ligand System", Beals, J. M., Darling, R. J., and Kuchibhotla, K., October 15, 2002 , Loras College, Dubuque, Iowa.

"Careers in Biochemistry", Beals, J. M., October 15, 2002, 2002 ITAG Young Scholars' Conference, Loras College, Dubuque, Iowa.

PATENTS

Numerous Patent Applications Filed

HONORS:

Scholarship Recipient - Loras College
Member of Delta Epsilon Sigma Honor Fraternity, Alpha Chapter - Loras College
Participant in National Science Foundation's Review Board for Undergraduate Research Programs, Denver, CO - Loras College, 1977
Presiding Member at the National Science Foundation's Winter Meeting for the Student-Oriented Studies Programs, Washington, D. C. - Loras College, 1978
American Heart Association's Paul A. Nicoll Fellowship - University of Notre Dame, 1984-1985

Arthur J. Schmitt Dissertation Year Fellowship - University of Notre Dame, 1985-1986
Rohm and Haas Graduate Student of the Year in Chemistry - University of Notre Dame, 1985-1986
National Institute of Health Postdoctoral Fellowship - Cornell University, 1987-1990
2500-Day Product Development Award - Eli Lilly & Co., 1995
Lilly Research Laboratories President's Recognition Award, 1995
Lilly Research Laboratories President's Recognition Award, 1997
Lilly Change the World Award, Q3'2002

SOCIETIES:

American Chemical Society
American Association for the Advancement of Science
New York Academy of Science

REFERENCES:

Dr. Francis J. Castellino, Dean, College of Science, Kleiderer-Pezold Professor of Biochemistry, Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556
(219) 239-6456

Dr. Harold A. Scheraga, Todd Professor of Chemistry, Department of Chemistry, Cornell University, Baker Laboratory, Ithaca, New York 14853-1301
(607) 255-4034

Dr. Bruce H. Frank
9377 Spring Forest Dr., Indianapolis, Indiana, 46260-1269
(317) 846-4233

Additional references available upon request.

POSTDOCTORAL RESEARCH SUMMARY:

The principle aim of my research at Cornell focused on the identification of potential chain-folding-initiation-sites (CFIS) and studying their contribution to the refolding of Ribonuclease A (RNase A). My work utilized a tryptic digest fragment identified as O-T-16, a C-terminal 20 amino acid peptide of RNase A. Theoretical predictions suggest that this hydrophobic region of RNase A is a potential CFIS and possibly dictates the intramolecular interaction necessary for rapid folding of RNase A. My results indicated the potential for a compact structure in O-T-16, with limited structural distributions observed under folding conditions.

My approach to this problem employed nonradiative energy transfer (NET) to ascertain distance constraints, from 15-70 Å, in O-T-16 under folding and unfolding conditions. This approach necessitated that site specific, stoichiometric chemical modifications be made to the peptide. The labeling involved extensive use of reverse-phase and ion-exchange HPLC. The interprobe

distances were determined by measuring the effects of nonradiative energy transfer on the fluorescence of the donor using both steady-state and lifetime decay experiments. The distance distributions in the structures, determined from the initial NET results, indicated that hydrophobic bonds play significant role in the expression of structure in this peptide under folding conditions.

My primary purpose for doing postdoctoral research in the area of protein folding was to learn more about protein structure in an attempt to assimilate and apply this information in the areas of protein-protein and protein-lipid interactions.

GRADUATE THESIS RESEARCH SUMMARY:

The principle aim of my graduate research at Notre Dame was to investigate the roles that acidic phospholipid, the protein cofactor, factor $VIII_a$, and protein structure of factors IX_a and X play in the assembly of the bovine intrinsic tenase complex. The study was an integrated one utilizing techniques used in both lipid and protein chemistry. My results showed that 1) domains of phosphatidylserine (PS) on the lipid surface are not necessary for vitamin-K dependent binding, 2) binding of factor IX_a and its activation products are PS concentration dependent, 3) two different kinetic models are required to explain activation of factor X in the presence and absence of factor $VIII_a$, and 4) the identification of factors IX and X as a+b proteins with secondary structure models determined using circular dichroism and a combined predictive algorithm.

The research approach required the isolation of blood coagulation factors VIII, IX, X, and XI purified to homogeneity using protein precipitation in addition to gel-permeation, ion-exchange, and affinity chromatography. These coagulation factors were activated and stabilized for binding studies and kinetic assays of the reconstituted factor X activating complex.

Phospholipid vesicles composed of phosphatidylserine and phosphatidylcholine were used as a lipid source. Physical properties of vesicles were defined in an attempt to understand the roles these properties play in the assembly of the complex. Properties studied included vesicle size, composition, and inner/outer head group ratios utilizing techniques of quasi-elastic light scattering (QELS), high performance liquid chromatography (HPLC), and fluorescence spectroscopy, respectively.

Calcium mediated binding studies of numerous blood coagulation factors to defined vesicles were performed using dynamic light scattering. In addition, the physical size of various proteins when bound to vesicles were determined using QELS. The kinetics of the reconstituted complex were studied utilizing a continuous coupled colorimetric assay.

The secondary structures of the protease and substrate of the tenase complex were studied utilizing a two-dimensional approach involving circular dichroism and empirical calculations. This technique integrated computerized algorithms that resulted in the development of an empirical predictive program designed for both micro- and mini- computers.

Finally, work not related to the above study, involved the development and use of monoclonal antibodies to study structure and function relationships in plasminogen. In addition, the

secondary structural elements of the kringle domains of plasminogen, tissue plasminogen activator, and prothrombin were determined.

II. Declaration of Dr. Ranmali Wijayaratne, submitted February 18, 2003.

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	James A. Hoffmann & Jirong Lu	)
Serial No.	:	09/928,198	)
Filed	:	August 10, 2001	) Group Art Unit: 1646
For	:	FSH Formulation	) Examiner: R. DeBerry
Docket No.	:	X-12383N	)

DECLARATION UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Arlington, VA 22202
Sir:

I, Ranmali Wijayaratne, hereby state and declare that:

1. I hold the degree of Doctor of Philosophy in Chemistry from the University of Maryland, College Park (1982).
2. I am currently a Research Scientist at Lilly Technology Center (Lilly), Indianapolis, Indiana. I have been a scientist with Lilly since February 1994 and have been involved with chromatographic analysis for numerous protein formulations.
3. I am co-author of 12 scientific publications in refereed journals.
4. I am not named as an inventor on any US patents or patent applications, including the present application.
5. My curriculum vitae is attached.
6. Attached are data from an experiment performed in a laboratory under my supervision. The goal of this experiment was to determine the effect of benzyl alcohol on the stability of a

formulation that contained an FSH variant that differed from human FSH only in lacking the last three amino acids of the beta subunit. The experimental design was to examine one factor with the others being fixed. The stability indicating assay utilized was size exclusion chromatography.

7. The formulations included the following ingredients in an aqueous diluent:

   Fixed factors: 50 μg/mL FSH variant, 15 mM citrate, 5.0% sucrose, 0.1% methionine, pH 7.0.

   Varied factor: 0.0% benzyl alcohol and 0.9% benzyl alcohol

8. The vials were stored at temperatures of 5°C, 25°C and 40°C, which represent the following three levels of storage temperature:

   Refrigerated conditions at 5°C (typically 2-8°C),

   Room temperature conditions at 25°C (typically between 20-25°C), and

   Accelerated conditions at 40°C (typically 37°C or above).

9. Samples were pulled from each vial at 0, 1, 2, 3, 4, 5, 7, 8, 10 and 12 weeks, and were analyzed for heterodimer content using size exclusion chromatography.

10. The size exclusion chromatographic (SEC) assay is stability indicating and is a measure of the % heterodimer, % subunits and the chemical potency (μg/mL). Duplicate injections into the HPLC were made from each vial at each time point. The HPLC instrumentation included HP1100 chromatography systems and the HP1000 chromatography data collection system.

11. The SEC-HPLC ambient assay conditions were as follows: Column type: TSK-GEL G2000SWxL, Flow Rate = 1.0 mL/min; Elution buffer = 0.1 M sodium phosphate, pH 7.4 (95%) and 5% isopropyl alcohol; temperature = ambient. UV detection was performed at 214 nm.

12. The assay method can readily detect heterodimer instability, and was validated according to ICH guidelines for Phase I clinical trials in terms of linearity, precision (repeatability), specificity, detection limit and quantitation limit, range, and accuracy.

13. Results for the experiment are shown in Table A.

Table A. Percent Heterodimer in FSH Formulation vs. Time and Temperature.

	40°C		25°C		5°C	
Weeks	FSH control	FSH + BzOH	FSH control	FSH + BzOH	FSH control	FSH + BzOH
0	96.19	96.42	96.19	96.42	96.19	96.42
1	95.67	94.21	-	-	-	-
2	94.31	89.55	96.28	95.89	-	-
3	93.58	88.53	-	-	-	-
4	93.48	88.37	96.49	96.57	96.51	96.5
5	93.2	90.2	-	-	-	-
7	-	-	95.78	95.18	-	-
8	-	-	95.78	95.20	95.83	95.66
10	-	-	95.99	95.44	-	-
12	-	-	-	-	96.09	95.79

From the data in Table A, I conclude that

14. At storage conditions 5°C and 25°C, the initial, 2, 4, 7, 8 and 12-week time point data for 0.0% Benzyl alcohol and 0.9% Benzyl alcohol were about the same with regards to percent heterodimer. Small differences observed were within the margin of error in the experimental method. There was significant degradation at 40°C at 2 weeks and beyond for samples with and without benzyl alcohol, but a faster rate of degradation with benzyl alcohol than without it.

15. The FSH variant formulation with benzyl alcohol is stable at both refrigerated temperature and at room temperature.

16. The FSH variant formulations with benzyl alcohol are pharmaceutically acceptable formulations that would be suitable for multiple dosing at both room temperature and at refrigerated temperature.

17. The FSH variant formulations with benzyl alcohol are sufficiently stable, with respect to heterodimer content, to provide a multi-dose pharmaceutical product.

18. The rate of heterodimer loss at room temperature is about the same with benzyl alcohol as without it, at both room temperature and at refrigerated temperature.

19. The presence of benzyl alcohol in these formulations permits FSH to be made available in pharmaceutically acceptable, multi-dose forms suitable for use at room temperature.

20. These data obtained with an FSH variant are representative also of the heterodimer stability of human FSH with benzyl alcohol.

I further declare that:

21. It would have been difficult to predict the effect of benzyl alcohol on stability of FSH formulations. If any prediction could have been made, it would have been that as temperature increased, any loss of heterodimer due to benzyl alcohol would likewise increase with temperature.

22. At 40 °C, benzyl alcohol accelerates heterodimer loss compared with the control lacking benzyl alcohol, whereas, at refrigerated temperature (5 °C) and at room temperature (25 °C), the stability of formulated FSH with and without benzyl alcohol is about the same.

23. I would have expected the rate of heterodimer loss in the FSH formulation containing benzyl alcohol at room temperature to be greater than what was actually observed, that is, to be more similar to the rate of loss observed with the FSH + benzyl alcohol formulation at (40 °C) than to the rate of loss observed at 5 °C.

I further declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both (18 U.S.C. 1001), and may jeopardize the validity of the application or any patent issuing thereon.

_____

Ranmali Wijayaratne, Ph.D.

_____

February 18, 2003

CURRICULUM VITAE

RANMALI D. WIJAYARATNE

ADDRESS: 534, Smokey Row Court
Carmel, IN 46033

PHONE: (317)- 277-2744 (Office)

EDUCATION/LICENSES

1973 B.S. (Chemistry-Honors) University of Sri Lanka, Colombo, Sri Lanka
1977 M.S. (Analytical Chemistry) North Carolina State University, Raleigh, NC
1982 Ph.D. (Analytical Chemistry) University of Maryland, College Park, MD
1993 MBA (with distinction) Keller Graduate School of Management, Chicago, IL

EXPERIENCE

2000- To Present
- **Analytical Team leader, Pharmaceutical Product Development, Eli Lilly Co., Indianapolis, IN**
Responsibilities include being the Team Leader representing all analytical activities on several protein or small molecule project(s). In addition to being on the "core" program team, directs the analytical activities to support the development of drugs through IND to NDA phases. Has developed excellent relations with Discovery and other functional areas by working in an interdisciplinary environment through good teamwork and communication and writing skills.

1998-2000
- **Development Project Manager, Lilly Corporate Center, Eli Lilly & Co, Indianapolis, IN**
Performed duties as the CM&C project Manager (Chemistry, Manufacturing and Control) for two early decision phase drug products. Project goals were met though coordinating and managing the CM&C functions of bulk manufacturing, analytical , formulation, regulatory, CT operations and included dealing with external partners.

1994-1998
- **Research Scientist, Research Technologies and Proteins, Eli Lilly and Co, Indianapolis ,IN**
Responsibilities included planning, organizing, and directing the activities of an analytical laboratory unit supporting fermentation and purification efforts of bulk drug development. These included developing robust and rugged methods for in-process assays with appropriate validation criteria and transfer to QC.

1987-1993
Head, Chromatography, Searle, Skokie, Il
Responsibilities included staffing and directing the an analytical

	laboratory unit supporting the discovery of new targets. Supervised technical personnel and had extensive "hands on" experience with modern technology in the characterization of small and large molecules.
1984-1987	**Research Investigator, Searle, Skokie, Il**
1982-1984	**NSF Post Doctoral Fellowship; National Center for Atmospheric Research, Boulder, Co**

Knowledge/Skills/Abilities/Strengths

Knowledge

- Analytical quality systems/method development
- Analytical protocol development, SOPs, method validation, knowledge of GMP and regulatory requirements
- Development Project Management and knowledge of overall drug development
- Familiarity with core therapeutic areas as it pertains to Discovery/Development
- Business Alliances; In addition to writing term sheets for contractual agreements knowledge of alliance management to effectively deal with third parties; Includes assessment of potential licensing opportunities (due diligence).

Skills/Abilities /Strengths:

- Good leadership skills; good scientific reasoning skills & problem solving skills;
- Good interpersonal skills; coaching and communication skills
- Good conflict resolution skills, negotiation skills and project management skills
- Ability to bring a business perspective to a scientific endeavor

Publications:
12 publications in refereed journals and 15 internal technical documents

There are no related proceedings.